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# ARCHIVES OF PATHOLOGY

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## THE PHYSIOLOGY OF VITAMINS

### V. CUTANEOUS MANIFESTATIONS RELATED TO A DEFICIENCY OF THE VITAMIN B COMPLEX \*

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AND

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There is a rather widespread belief that a liberal intake of the vitamin B complex<sup>1</sup> is important in preventing the development of various lesions of the skin. The basis for such a belief is probably to be found in the reports of favorable results in such cases following the administration of yeast. This, coupled with the fact that yeast is a good source of vitamin B, led to the conclusion that vitamin B is the factor responsible for the therapeutic results. Records of observations indicating such a relationship in either human beings or lower animals that were subsisting on rations carefully controlled in content of vitamin B and complicated as little as possible therapeutically by dietary variables, are scarce. Hawk and his associates<sup>2</sup> carefully reviewed the literature concerning the therapeutic uses of yeast, and reported their own observations on ninety-one cases. Their numerous tables indicate that yeast may be administered to advantage in cases of furunculosis, acne and constipation. Valuable as these observations are, they do not allow the conclusion that the vitamin B in yeast is responsible for the beneficial effects obtained. The general results reported by Hawk and his associates were subsequently confirmed by Welker and Heintz.<sup>3</sup>

The literature concerning the antineuritic vitamin as studied in different species of animals does not make any point of the cutaneous manifestation of a deficiency of vitamin B. Likewise, the literature on

\* Submitted for publication, Aug. 2, 1928.

\* From the Laboratory of Physiological Chemistry, Yale University.

1. The substances containing vitamin B used in these experiments contained both the antineuritic and the heat stable components of this vitamin. Therefore, the expression "vitamin B complex" is used. The basal ration was relatively free from both of the B fractions just named.

2. Hawk, P. B.; Knowles, F. C.; Rehfuess, M. E., and Clark, J. A.: The Use of Bakers' Yeast in Diseases of the Skin and of the Gastro-Intestinal Tract, J. A. M. A. 69:1243 (Oct. 12) 1917.

3. Welker, W. H., and Heintz, E. L.: Arch. Therap. 5:152, 1926.

beriberi, although mentioning the occasional occurrence of lesions of the skin, does not emphasize them as characteristic elements of the syndrome. It may well be questioned whether the beneficial effects attributed to the administration of yeast are really due to the vitamin B involved. The fact that among the many clinical conditions tested by the therapeutic administration of yeast, only furunculosis, acne and constipation should yield at all readily to such treatment, suggests that the primary cause of the improvement in such cases is to be sought in such factors as change of the intestinal flora, diminution of putrefaction and enhancement of intestinal motility. In other words, yeast may be regarded as achieving results as do most so-called "blood purifiers," namely, by altering and improving conditions in the lower part of the alimentary tract.

More recently, the value of a concentrate of vitamin B in the treatment of pellagra was reported by Goldberger and his associates.<sup>4</sup> It is pertinent to the theme of this paper to mention the fact, well recognized by clinicians, that dermatitis is part of the syndrome characteristic of pellagra. In the studies of Goldberger and his co-workers, it appears that there is evidence that a deficiency of what has been spoken of hitherto as vitamin B may be a factor in the development of certain lesions of the skin.

According to Gerstenberger,<sup>5</sup> vitamin B has an unmistakably curative effect in cases of herpes stomatitis and herpes labialis. Lesions of these conditions in thirteen children and one adult yielded in remarkable fashion to the oral administration of a concentrate of vitamin B. Other dietary variables of the nature of vitamins were ruled out as therapeutic factors by the fact that the curative concentrate contained only the vitamin B complex.

In the course of nutritional experiments carried out by one of us (G. R. C. during 1923-1924) there appeared in dogs subsisting on artificial rations (tables 1 and 2) two well defined cases of ulcers, which were formed particularly on the bony prominences of the lower fore limbs. The fact that the dietary histories of the animals that showed such lesions were known for long periods—from seven months to more than a year—gave to these observations a unique significance. However, the scars of presumably the same lesions were also observed frequently in other dogs of our colony that were not subjects of nutritional experiments. More recently, two of us (C. J. S. and W. B. R.), in three series of experiments, placed groups of dogs on a regimen deficient

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4. Goldberger, J., and Lillie, R. D.: U. S. Pub. Health Rep. **41**:1025, 1926. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: U. S. Pub. Health Reprint no. 1062, p. 297, 1926.

5. Gerstenberger, H. J.: The Etiology and Treatment of Herpetic (Aphthous and Aphtho-Ulcerative) Stomatitis and Herpes Labialis, *Am. J. Dis. Child.* **26**:309, (Oct.) 1923.

in vitamin B, with a view to studying the changes in the blood and the gastro-intestinal tract and other changes associated with such a dietary condition, and in the course of these investigations they noticed in certain animals the appearance of similar lesions of the skin.

#### THE LESIONS

Figures 1 and 2 show early and late stages of the lesions. Through the courtesy of Dr. M. C. Winternitz of the Department of Pathology of the Yale University School of Medicine, who observed the lesions and arranged for their reproduction in colors, we are able to give the following description:

The illustrations amply portray the details of the anatomic lesions, in both the early and the late stages. It is obvious that these lesions were usually symmetrically placed; that they involved particularly the bony prominences, on both the flexor and the extensor surfaces of the fore and the hind limbs. The lesions were invariably round or slightly oval. In the early stages, they appeared slightly elevated, pink and denuded of hair. Gradually, the elevated zone was sloughed

TABLE 1.—Casein Diet III \*

Components	Grams	Calories	Per Cent
Casein, commercial (12.7 per cent nitrogen).....	6.3	20.6†	41.2
Sucrose.....	4.5	18.0	29.4
Lard.....	2.8	25.2	18.3‡
Butter.....	1.1	9.0‡	7.2‡
Bone ash.....	0.4	....	2.4
Salt mixture§.....	0.2	....	1.3
Total.....	15.3	72.8	100.0

\* One kilogram of this food contains 0.8 Gm. of nitrogen and 73 calories, 46.5 per cent of which are furnished by fat. A discussion of the kilogram unit may be found in Cowgill: J. Biol. Chem. 56: 725, 1923.

† Calculated on a basis of 81.9 per cent protein.

‡ Figured as containing 90 per cent fat.

§ The salt mixture was made as follows: sodium chloride, 10 Gm.; calcium lactate, 4 Gm.; magnesium citrate, 4 Gm.; ferrie citrate, 1 Gm., and iodine-potassium iodide solution (Lugol's), a few drops.

away, leaving behind a sharply punched-out ulcer, very similar indeed to the gastric ulcer, as it appears in man. Their appearance was as though a sharp instrument had been used in punching out the holes. They differed from the gastric ulcer in that they were not terraced but had precipitous sides. In the course of the formation of the ulcer from the early to the late stage, as is indicated on the hind quarter (right) in figure 2, the center of the elevated zone first sloughed away, and the sloughing gradually extended to the margin of healthy tissue. When the ulceration was completed, the base was brilliant red, smooth and clean, and, as soon as the necrotic material had been eliminated, this clean appearance remained. Accumulations of exudate were not encountered. This may have been due to the constant licking of the sores by the animal.

#### REPORT OF CASES

*First Group, 1924.*—CASE 1.—Dog 55, a female mongrel, weighing 7.5 Kg., received casein diet III (table 1) plus 0.6 Gm. per kilogram each day of "Vitavose" \*

6. Obtained from the Ward Baking Company, New York. Now obtainable from E. R. Squibb & Son, New York.

(a commercial product rich in vitamin B). The animal was in excellent condition and maintained a good appetite, eating all the food offered for 262 days (approximately eight and two-thirds months), which was the length of the period during which the basal diet was supplemented by the source of vitamin B (period 1). The body weight at the end of period 1 was 9.8 Kg. During period 2, the daily supplement of "Vitavose" was omitted. Complete, voluntary ingestion of all food offered occurred for fifty-seven days. From then on, the appetite was capricious, and a lethargy developed associated with conjunctivitis and the appearance of sores on the bony prominences of the limbs. The body weight was 8.3 Kg. on the ninety-first day. On the ninety-second day of this period, the spastic paralysis characteristic of advanced deficiency of vitamin B appeared. "Vitavose" was administered by stomach tube repeatedly, but the material was not retained. Death resulted. Autopsy revealed lobar pneumonia as a complication.

CASE 2.—Dog 56, a female mongrel of the fox terrier type, weighing 6.1 Kg., received meat residue diet IV (table 2) plus 0.6 Gm. per kilogram per day of "Vitavose," the latter administered separately. The animal ate all food offered

TABLE 2.—Meat Residue Diet IV\*

Components	Grams	Calories†	Per Cent
Meat residue : {13 per cent nitrogen.....}	6.15	{ 21.6 }	{ 37.3 }
{10 per cent fat.....}		{ 5.67 }	
Sucrose.....	5.68	23.5	34.1
Lard.....	3.00	23.4	18.2
Butter.....	1.12	9.46‡	6.7
Bone ash.....	0.4	.....	2.5
Salt mixture§.....	0.2	.....	1.2
Total.....	18.50	88.6	100.0

\* One kilogram of this food contains 0.8 Gm. of protein nitrogen; 1 Gm. contains 5.68 calories.

† Loowy's factors are used, namely, 4.32 for protein, 4.18 for carbohydrate and 9.46 for fat.

‡ From the Valentine Meat Juice Company, Richmond, Va.

§ A 10 per cent correction for the salt and water content.

# Salt mixture given in table 1.

and remained in an excellent nutritive state for the entire period of 230 days—approximately seven and two-thirds months. At the end of period 1, the body weight was 6.8 Kg. During period 2, the daily administration of "Vitavose" was omitted. Seven days later, the animal showed the first sign of anorexia. The dog had a capricious appetite for the next twenty-eight days. The animal was then given one large dose of "Vitavose." This was followed by a perfect intake of food for eight days, after which the appetite again became erratic. Another single dose of the material containing vitamin B was associated with a restoration of appetite for a period of seven days. The dog was then given casein diet III, without the supplementary vitamin, for a period of sixty-three days. The appetite was capricious during this time. The preulcerative condition portrayed in figure 1 was noticed. The dog weighed 6.1 Kg. Otherwise, the nutritive condition of the animal appeared satisfactory. When the diet was rendered adequate by supplying the missing vitamin separately, the intake of food again became complete, and the preulcerative lesions improved: horny dry scablike tissue, presenting the general appearance of a scar, was the only sign of the sores.

In the case of dog 56, there was presented, quite apart from the particular theme of this paper, a perfect demonstration of the validity of the hypothesis that a deficiency of vitamin B is associated with certain pathologic conditions. For over seven months this animal was maintained in excellent condition, as far as one could judge from appearances, with a perfect voluntary intake of food,





Fig. 1.—Symmetrically placed lesions on the fore limbs of a dog subsisting on rations deficient in vitamin B. The early stage of the sores is depicted.





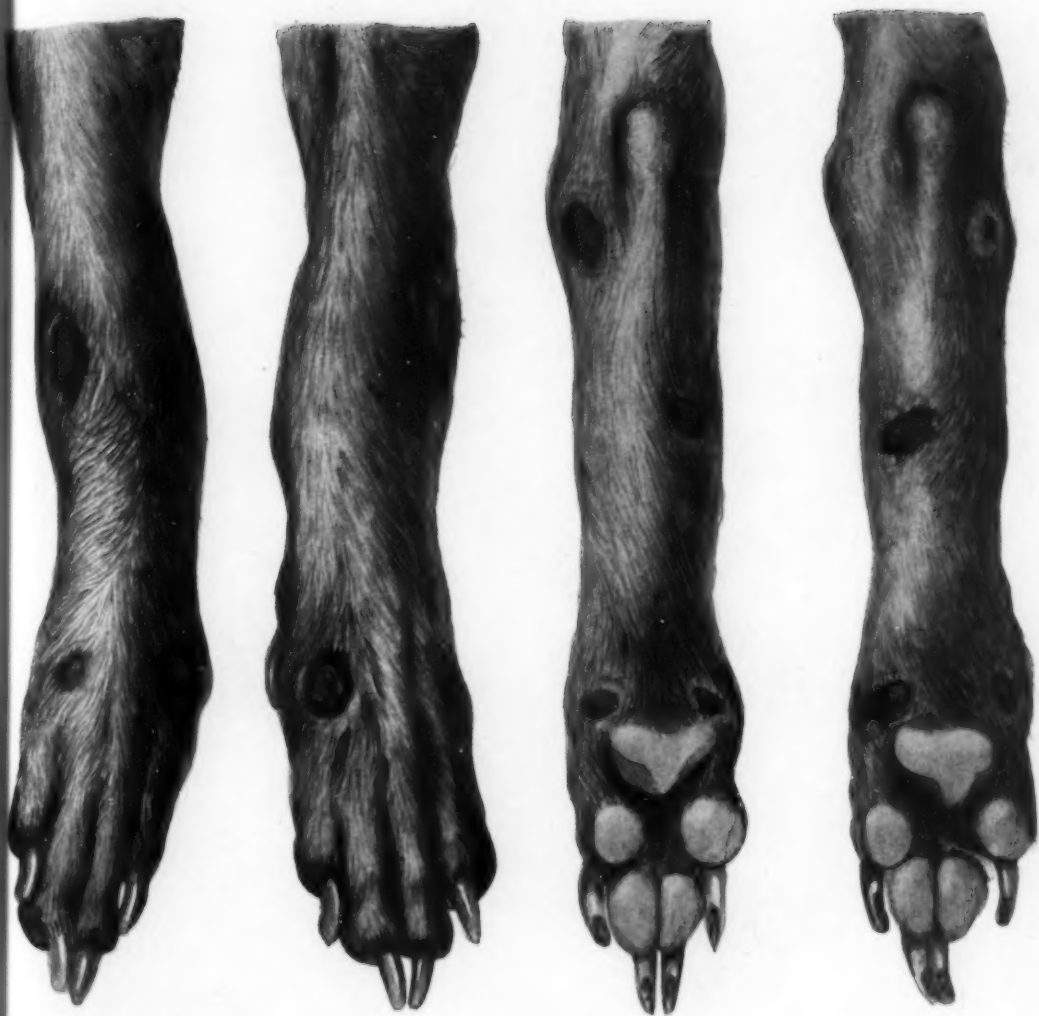


Fig. 2.—A later stage of the lesions due to deficiency of vitamin B. The center of the elevated zone shown in figure 1, first sloughs away, as shown here on the right hind quarter, and the sloughing gradually extends to the margin of healthy tissue, leaving a smooth, clean brilliant-red base.



on a basal ration free from vitamin B, supplemented by a carefully measured amount of a material containing vitamin B. On merely withholding the supplementary vitamin, making no other change in the dietary conditions, we were able to bring about, after approximately a week, a loss of appetite in the animal; and, conversely, we were able promptly to correct this loss of appetite by a separate administration of a single dose of the material containing the vitamin. A second loss of appetite was corrected in similar fashion.

*Second Group, June, 1926, to August, 1927.*—CASE 3.—This case occurred in the first series of experiments with casein diet III. Ulcers on the ear of a dog were first noticed on the twenty-first day of the period of deprivation of vitamin B. These ulcers grew worse, and others appeared on different parts of the body, especially the joints and the feet. Local treatment with mercurochrome-220 solution and other applications was little, if at all, effective. A remedy for mange and frequent baths seemed to effect improvement in the condition of the skin only temporarily. Generalized so-called "polyneuritic" symptoms characteristic of advanced cases of a deficiency of vitamin B appeared on the sixty-second day of the deficiency regimen. Therapeutic treatment with vitamin B was instituted, a commercial "yeast vitamin powder (Harris)"<sup>7</sup> being used. The nervous and muscular symptoms soon disappeared. On the eighty-fourth day of the experiment—the twenty-second day after the first administration of vitamin B—the animal was apparently normal. The sores had healed.

CASE 4.—Case 4 occurred in the second of three series of experiments with casein diet III. An ulcer on the plantar surface of the forepaw of a dog was first noticed on the thirty-ninth day of the regimen deficient in vitamin B. The animal's general condition grew worse, and more ulcers appeared on other parts of the body. Both forepaws were ulcerated on the forty-fourth day. Obvious changes in the dog's general condition did not appear until the sixty-sixth day; on that day, the animal died, after exhibiting severe symptoms of "polyneuritis." Several doses of material that contained the vitamin were administered by mouth before death, but all were vomited.

CASE 5.—Case 5 occurred in the second of the three series of experiments with casein diet III. Ulcers on bony prominences of the limbs of a dog were first noticed on the thirty-sixth day of the regimen deficient in vitamin B. The sores continued and grew somewhat worse. On the sixtieth day, the animal died suddenly with symptoms of advanced deficiency of vitamin B.

CASE 6.—This case occurred in the third series of experiments with casein diet III. Ulcers on the limbs of a dog were first noticed on the twenty-eighth day of the deficiency of vitamin B. The sores increased in number and grew worse until, on the forty-first day, they were present on the bony prominences of both fore limbs, the most serious lesions being at the elbow. "Polyneuritic" symptoms appeared on the forty-third day. Vitamin B was administered therapeutically with success. On the sixty-sixth day, the animal still showed a general erythema. The blood sugar level was normal. On the seventy-first day of the experiment—the twenty-eighth day of the treatment with the vitamin—a general erythema somewhat characteristic of mange was still present, but the ulcers on the bony prominences of the limbs had disappeared.

CASE 7.—This case occurred in the third series of experiments with casein diet III. One large ulcer on the thigh of a dog was noticed on the sixtieth day of the deficiency of vitamin B. It showed a remarkably clean base; evidence of local infection was absent during its development. It appeared to come suddenly

7. From the Harris Laboratories, Tuckahoe, N. Y.

as a large exfoliation of a slough. The ulcer was about the size of a fifty cent coin. The edges of the ulcer were not edematous, red or inflamed, hence not apparently infectious in nature. Determinations of the blood sugar revealed normal values throughout. The animal died suddenly on the sixty-seventh day of the deficiency regimen, before therapy with vitamin B was effective. The dog used as a control on the water and the food regimen did not manifest any gross morbid changes in the epidermal structures.

**ADDITIONAL CASES OF INTEREST.**—Two animals that had served as the subjects of a research in the Department of Pathology had been fed for a considerable period on a diet of commercial dog biscuit. These dogs, after a time, developed anorexia, became exceedingly thin and showed ulcers of the type described in this paper. Each dog was then given daily several large doses of a yeast vitamin concentrate. One animal failed to show any improvement; its urge to eat could not be restored, with the result that the starvation continued and the animal eventually had to be put to death. The other dog received two of the daily dosages of vitamin before it recovered its desire to eat. The improvement in the condition of the ulcers was obvious before the animal had eaten much food. This result suggested that the curative effect of the preparation administered was attributable to the vitamin contained therein rather than to the general improvement of the nutritive condition associated with the intake of food following a restoration of appetite.

#### COMMENT

Two of our animals developed the sores after approximately a month of subsistence on the diet deficient in vitamin B, and treatment with a concentrated preparation of vitamin B resulted in the healing of the lesions. Animal 3, after a period of rest on an excellent diet, was again placed on the diet deficient in vitamin B, and thirty-nine days later it again exhibited the sores (case 4). This parallelism between the subsistence on diets deficient in vitamin B and the development of the lesions is worthy of emphasis.

In seeking an explanation why these lesions did not appear in all the animals subjected to the experiments, we were impressed with the consideration that the factor of local injury—pressure (?) in these cases—might have been variable, some dogs lying down for a greater part of the time than others.

The absence of gross evidence of local congestion, edema, excessive heat, tenderness and other signs of an inflammatory process in these lesions particularly emphasized the malnutritional rather than the inflammatory character of the lesions.

The reader may ask whether our data enabled us to relate the lesions at all specifically to the heat-labile antineuritic fraction of the vitamin B complex or to the heat-stable growth promoting substance. In answer, we can state only that both of the materials used as sources of vitamin B in these experiments, namely, Harris' "Yeast Vitamine Powder" and "Vitavose," have been shown to be capable of supporting growth in young rats fed on a diet adequate except for what up to the present has been called vitamin B.

These observations may prove of clinical value. As is well known, chronic invalids subsisting on a "hospital" diet are particularly prone to develop decubital ulcers, which are discouragingly resistant to treatment by the usual methods employed. Our observations suggest that more attention should be paid to the content of vitamin B in the diets used in such cases. Concentrates of vitamin B are now available commercially. Such preparations added to the routine diet may possibly prove of therapeutic value, and will probably improve the patient's appetite. In this way, the general nutritive state of the patient may be improved and healing favored.

#### SUMMARY

Lesions of the skin, frequently symmetrical, were observed in six dogs subsisting for long periods on artificial diets adequate except for the vitamin B complex. In two animals, the administration of a preparation rich in vitamin B was followed by a definite healing of these sores without any other treatment. One dog, after approximately a month's subsistence on the deficient diet, developed what appeared to be preulcerative stages of such lesions. The administration of the vitamin corrected the partial anorexia and checked the further development of the potential sores. The remaining three animals died suddenly of deficiency of vitamin B before treatment with the vitamin was effective.

The relation of the individual components of the vitamin B complex to such lesions of the skin remains to be determined.



# THE EFFECT OF CERTAIN TOXIC SUBSTANCES IN BACTERIAL CULTURES ON THE INTESTINAL MOVEMENT

II. EFFECT OF FILTRATES OF YOUNG CULTURES OF THE COLON-  
TYPHOID GROUP OF ORGANISMS ON THE INTESTINAL MOVE-  
MENT OF RABBITS AS RECORDED BY A NEW CINEMA-  
TOGRAPHIC METHOD; CORRELATION OF THIS EFFECT  
WITH THE PRODUCTION OF FOOD POISONING  
BY MEMBERS OF THIS GROUP \*

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AND

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CLEVELAND

In a previous study, Ecker and Rademaekers<sup>1</sup> showed the effect of filtrates of young broth cultures of *Salmonella ærtrycke* on the motility of segments of the small intestines of rabbits in situ in the living animal. It was found that a strong and gradual rise of the diastolic and systolic tone occurred; i. e., spasmodic contraction of the intestinal muscle. In their report, it was stated that with Sollmann and Rademaekers' modification of the Baur technic the stimulation of the longitudinal muscle was accompanied by a strong stimulation of the circular muscle and, therefore, also by increased propulsion of the intestinal contents. Broth alone failed to induce the reaction. In that study, only the ærtrycke type of bacilli was used. In the work presented in this paper, however, all the most important members of the colon-typhoid group of organisms were employed. Furthermore, the technic was completely revised to avoid the use of urethane for the anesthetic, and large quantities of Locke's solution. Dr. Torald Sollmann suggested the use of liquid petrolatum instead of Locke's solution. The newer method also permitted observations of the larger portion of the alimentary tract without its normal position and relationships being disturbed. The intestinal movements were recorded with a 16 mm. Bell and Howell motion picture camera. Finally, we attempted to correlate the new observations with the known activity of the group in the production of acute gastro-intestinal disturbance in man and animal.

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\* Submitted for publication, Sept. 5, 1928.

\* From the Departments of Pathology and Pharmacology, Western Reserve University School of Medicine.

1. Ecker, E. E., and Rademaekers, H.: J. Exper. Med. **43**:785, 1926.



## METHOD

Nineteen strains of the organisms were employed. The typhoid strains were newly isolated and were used after five transfers. An original *aërtrycke* (de Nobele) was also used. The organisms were grown for from seventeen to twenty-four hours at 37 C., on 2 per cent Witte peptone veal infusion broth with a  $p_H$  of  $\pm 7$ . The cultures were then filtered through a Berkefeld N candle, and a portion of the filtrate was always used immediately thereafter for intravenous injection. The remainder was discarded. Sterile pure broth filtrates were injected for controls in a number of animals, and a reaction was not seen in any case except in one animal which had been on a diet of green vegetables.

Animals that showed the slightest evidence of a gastro-intestinal disturbance were not used. One half of the animals, twenty, were used for controls to determine the toxicity of the filtrates in the whole animal. The other group of twenty animals were etherized and their spinal columns severed by crushing in the lower thoracic region, hemorrhage being avoided. This rendered insensitive practically the entire ventral abdominal wall of the animal. From one to two hours or more

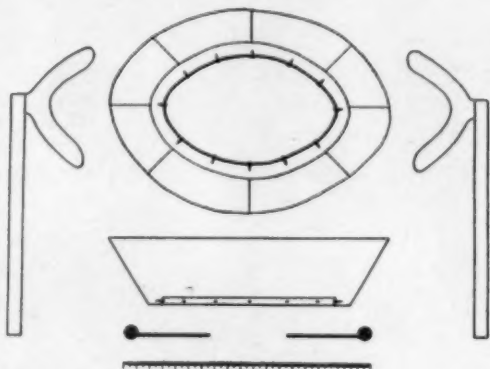


Fig. 1.—Diagram of the trough and supports used for the observation of the intestines of the rabbit in situ. The scale is in millimeters.

were allowed to elapse following the animal's recovery from the ether before laparotomy was performed.

Laparotomy was done as follows: The hair on the abdomen was clipped closely and petrolatum applied. A median incision about 15 cm. in length was made through the skin of the abdomen and the skin dissected free from the underlying muscle. The skin was then hooked back over the ring at the lower rim of a bottomless trough, which, for photographic reasons, was dull black, with dimensions as denoted in figure 1. The trough was then raised on its supports (figs. 1 and 2) and the pouch thus formed was filled with liquid petrolatum at 38.5 C. The petrolatum previously applied assisted in making a leak-proof seal around the bottom of the trough and prevented hair from floating into the oil. A second incision was then made through the linea alba, and the muscle and peritoneum were hooked back over the ring. If necessary, sufficient oil was added to cover the intestines in order to avoid confusing reflections from the surfaces exposed to the air. If the cecum or colon, or both, were found distended with gas and floating above the surface of the oil, catheterization was resorted to for emptying the colon, and a hypodermic syringe was used for emptying the cecum, puncture of the

blood vessels being avoided. This was necessary in about one half of the animals. The small intestine was not in any event disturbed.

As a rule, the intestine remained quiescent for from ten to fifteen minutes following laparotomy. Then rhythmic longitudinal muscle movements (pendulum) appeared in the small intestine. Mechanical stimulation was avoided as much as possible. This in the case of the small intestine, was never seen to cause excitation but frequently caused depression for short periods.

Injection of the filtrates was made in the posterior auricular vein.

For lighting and maintaining a constant temperature we used a 15 ampere direct current carbon arc lamp with a single 4 inch (10.16 cm.) condensing lens, which rendered the light beam approximately parallel. The beam was reflected from a mirror into the trough (fig. 2). This gave sufficient illumination for cinematography and provided just sufficient heat to maintain a constant temperature (38.5 C.) in the pouch, in a room where drafts were avoided. By shutting off the arc for short periods or using a 40 candle power carbon filament lamp in front of a

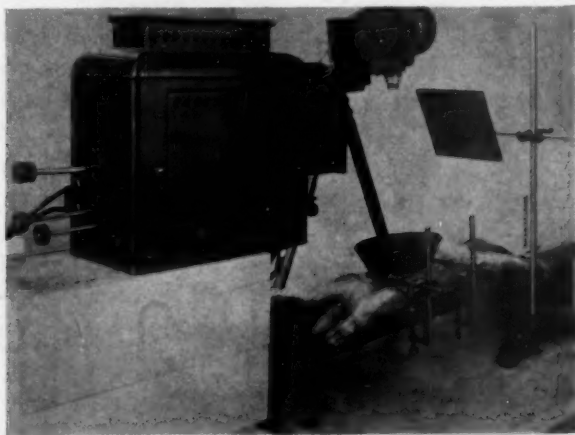


Fig. 2.—The arrangement of the apparatus for making a moving picture of the intestines of the rabbit in situ. A 15 ampere D. C. arc is used for illumination. A 6 inch (15.24 cm.) square mirror reflects the light into the trough. The camera is supported on a tripod with a tilting top.

reflector, the temperature of the oil in the trough was carefully controlled and was not allowed to vary more than 1 degree; but such procedures were seldom necessary.

The camera was fixed at a distance of about 15 inches (37.54 cm.) directly above the trough and centered by the use of a gun-sight. Ordinarily, from one-half hour to one hour was allowed to elapse after laparotomy; then a cinematographic picture of the normal activity of the intestines was taken. This procedure was adopted as routine. Following this, the filtrate was injected in doses varying from 3 to 4 cc. Uninterrupted observations were then carefully made for as long as four hours thereafter. Cinema pictures were taken whenever a definite change occurred. Ordinarily, violent reactions were noted when the filtrate was effective. Some animals were given normal broth about two hours prior to the injection of toxic filtrate, as indicated in table 1. One control rabbit exhibited an incomplete peristaltic rush following the injection of the plain broth.

This occurred in the early spring when fresh vegetables had been given to the animals. Other control animals did not exhibit the phenomenon either normally or following the injection of the plain broth.

Table 1 is a compilation of the results obtained with nineteen strains of organisms.

#### OBSERVATIONS

In these experiments, as stated, seven important subgroups of the colon-typhoid bacilli were studied. Three strains of *Eberthella typhi*, two strains of *Salmonella paratyphi* A, three strains of *S. enteritidis*, two strains of *S. schottmülleri*, four strains of *S. aertrycke*, two strains of *S. suipestifer* and three strains of *Escherichia communior* were used. The filtrates of young cultures of all these organisms were injected into a series of normal rabbits (denoted A in table 1) and the effects observed. The same filtrates then were injected into a second series of laparotomized animals (denoted B in table 1). Six rabbits, reported in table 1, and three others in the experimental series each received 3 or 4 cc. of plain broth about two hours prior to the injection of the toxic filtrates. We also gave two injections of plain broth but did not in any instance observe an effect that was abnormal. The plain broth was therefore harmless. We also observed normal rabbits for possible spontaneous reactions, but saw only normal rhythmic longitudinal movements and occasional peristalsis.

Meltzer and Auer<sup>2</sup> first introduced the term "peristaltic rush," in 1907. Before this, in 1872, the phenomenon had been described by van Braam van Houkgeest<sup>3</sup> as "Rollbewegungen." As stated by Meltzer and Auer, it is "a rapidly progressing wave of contraction preceded by a completely relaxed long section of the intestine through which fluid contents mixed with gas bubbles is rapidly driven. A complete peristaltic rush is one which sweeps down from the duodenum to the coecum without stopping." "Each coil, as the rushing wave passes through it, gives the appearance of a rapidly turning wheel."

Meltzer and Auer<sup>2</sup> did not see a rush in the opened abdomen of a normal rabbit. They also realized that "an opened abdomen is not a normal state." Alvarez and Mahoney,<sup>4</sup> however, claimed to have seen "good rhythmic movements and good spontaneous rushes shortly after the animals are opened." We saw an incomplete rush in only one supposedly normal rabbit injected with plain broth and this only when about two hours had elapsed following laparotomy. Rhythmic movements in the small intestine, and frequently also propulsion in the lower colon, were always seen by us in normal rabbits immediately following the operation, but spontaneous rushes were not seen.

2. Meltzer, S. J., and Auer, J.: Am. J. Physiol. **20**:259, 1907.

3. Van Braam van Houkgeest: Arch. f. d. ges. Physiol. **6**:266, 1872.

4. Alvarez, W. C., and Mahoney, L. J.: Am. J. Physiol. **69**:211, 1924.

TABLE 1.—General and Intestinal Reactions Produced in Rabbits Following Intravenous Injection of Young Culture Filtrates of the Colon-Typhoid Group of Organisms

Organism Used	Strain	Weight of Control Rabbit, Gm.	Age of Rabbit, Hours	Dose of Filtrate Injected, Cc.	Effect of Filtrate on Normal Control Rabbit (A)	Weight of Laparotomized Rabbit, Gm.	Observed Reactions of the Intestines in the Laparotomized Rabbit After Injection of Filtrate (B)	Summary of Intestinal Reactions
Eberthella typhi (all newly isolated organisms received from Dr. Charles Krumwiede)	E	2,100	17	4	1:10 slight defecation; 1:20 depression, rapid respiration and urination. Survived	2,250	0:50 rapid respiration; 1:00 rapid, irregular respiration; 1:07 mild peristalsis in colon; 1:20 few fecal balls; quiescent thereafter	No definite excitation
	G	1,000	19	3, A; 4, B (in A 2 hr. 10 min. and in B 1 hr. 55 min. after injection of 4 cc. plain broth)	0:40 defecation; 0:45 considerable depression, urination. Survived	2,300	0:25 rapid respiration; 0:55 mild pendulum movements in small intestine; 1:00 circular contractions of middle colon, complete relaxation of small intestine; 1:10 ceum showed mild circular contractions and remained in fairly high tone; 1:15 middle colon spastic, showed longitudinal striations; 1:12 few fecal balls	No definite excitation
	E	1,300	23	3 (in A 2 hr. and in B 2 hr. 6 min. after injection of 3 cc. plain broth)	0:30 urination; 0:40 slight depression, defecation. Survived	1,380	During two hours' observation, no change from normal	No definite excitation
Salmonella paratyphi A (stock strains)	O	2,000	17	4	0:55 urination; 0:07 mild diarrhea, depression; 0:70 rapid respiration, prostration, severe diarrhea; 1:25 improved. Survived	2,170	0:12 normal pendulum movements of small intestine; 0:15 normal haustral movements in colon; 0:42 animal appears restless, lower colon spastic; 0:44 progressive increase of tone in small intestine; 1:00 part of small intestine appeared spastic and remained so	Mild effect on circular musculature
	L	1,050	18	3	0:30 urination; 0:35 prostration, rapid respiration, diarrhea; 0:45 to 1:00 severe diarrhea; 1:45 depression. Survived	1,700	1:12 marked peristalsis in ceum and peristaltic rush in upper colon, lower colon spastic; 1:25 marked circular contractions in uterus; 1:33 longitudinal striations in small segment of colon, few fecal balls; 1:44 peristaltic rush in colon followed by rush in ileum filling ceum, followed by marked peristalsis; 1:48 antiperistalsis in colon, ceum movements, more defecation; 1:49 another peristaltic rush in colon contents fluid; 1:53 death in asphyxial convulsions (inspiratory spasm of diaphragm occurred prior to convulsions)	Peristaltic rushes in colon and in ileum

Salmonella typhimurium (Gärtner)	Wallasey (This was used in outbreak of food poisoning; the strain was supplied by Mr. Bruce White)	1,750	18	3 (in B & T)	0:10 rapid respiration, restles; 0:50 rapid respiration; 1:10 prostration, 1:30 consider- able defecation. Survived	2,100	1:12 peristaltic rush throughout small in- testine; defecation similar to control rab- bits; a rush was observed in peristaltic rushes were observed in them completely emptying the small in- testine into the cecum. Colon spastic, show- ing haustral movements in middle colon. Seventeen minutes after last rush, upper colon was dilated and showed kneading movements	Peristaltic rushes in small in- testine
	Deil (This was isolated at Deil, Su- matra, and supplied to us by Prof. E. P. Snyders)	1,550	18	3	1:00 marked prostration, urination and severe diarrhea. Survived	2,130	1:02 peristaltic rush in small intestine; 1:10 second rush (incomplete); 1:12 diarrhea; 1:27 third rush; 1:29 rush of upper small intestine and middle colon; animal died 1:44	Peristaltic rushes in small intestine and in middle colon
	Danysz 304 (A "Danysz" bacillus isolated by R. S. Spray from com- mercial rat virus A.T.C.C.)	1,770	23	3.5	0:47 prostration, severe diarrhea. Survived	2,160	0:40 peristaltic rush in upper small intestine followed by another one minute later (both incomplete); 0:50 peristaltic rush in colon; 0:52 second rush in colon; 1:07 per- istaltic rush in small intestine filling cecum followed by rush in colon and defe- cation, respiration rapid and "jerky"; 1:19 more defecation	Peristaltic rushes in small in- testine and in colon
Salmonella schottmüller	209 (rough strain from single cell culture)	1,600	18	3	0:49 urination; 0:50 prone; 0:50 defecation; 0:58 diarrhea; 1:05 more diarrhea (without marked prostration). Survived	2,400	0:25 strong contractions of uterus; 1:13 restless; 1:20 lower colon spastic; 1:30 lower colon showed contractions; intestine and uterus quiescent thereafter	No definite excitation
	B12 (both from col- lection of Prof. E. O. Jordan)	2,220	20	3	0:50 rapid respiration, depressed; 0:55 diarrhea; 1:05 complete pros- tration. Survived	1,710	0:33 marked pendulum movements through- out small intestine; 0:38 respiration deeper and more rapid; 0:48 pendulum move- ments very strong; 1:08 lower colon quite active, respiration "jerky"; 1:13 strong propulsion in lower colon, middle colon spastic; no change thereafter	No definite excitation
Salmonella aërycke	186 (J. Infect. Dis. 21: 541, 1917)	1,700	24	3	0:45 prostration, urination, no diarrhea; 1:00 death in asphyxial convulsions	1,000	0:30 pendulum movements beginning in upper intestine; 0:45 respiration rapid and labored, marked peristalsis in upper colon; 0:55 defecation and urination; 1:20 respi- ration slower and deeper, peristaltic rush in small intestine followed by flaccidity; 1:24 strong peristalsis throughout small intestine; 1:26 death	Peristaltic rush through- out small intestine
	180 (J. Infect. Dis. 21: 541, 1917)	2,000	18	4	0:43 prostration, urination; 0:46 rapid respiration, remained pros- trated for some time. Survived	2,205	0:57 rapid respiration; 0:59 dyspnea; 1:17 peristaltic rush throughout small intestine followed by flaccidity, entire colon spas- tic; 1:22 second rush; 1:37 peristalsis in colon, upper part dilated; 1:45 third rush through small intestine, peristalsis in colon; 1:52 death in asphyxial convulsions	Peristaltic rushes throughout small in- testine



TABLE 1.—General and Intestinal Reactions Produced in Rabbits Following Intravenous Injection of Young Culture Filtrates of the Colon-Typhoid Group of Organisms—Continued

Organism Used	Strain	Weight of Control Rabbit, Gm.	Age of Culture, Hours	Dose of Filtrate Injected, Cc.	Effect of Filtrate on Normal Control Rabbit (A)	Weight of Laparotomized Rabbit, Gm.	Observed Reactions of the Intestines in the Laparotomized Rabbit After Injection of Filtrate (B)	Summary of Intestinal Reactions
Salmonella aertrycke (continued)	688 (Carl Ten Broeck's strain, isolated from rabbits, "Rabbit typhoid no. 104," A.T.C.C.)	1,080	17	4	0:10 defecation, distress; 0:15 prostration; 0:50 respiration rapid and labored. Survived	1,760	0:45 marked cecal movements; 1:00 peristaltic rush throughout small intestine; 1:38 defecation	Peristaltic rush throughout small intestine
	de Nobele (from Prof. E. P. Snyders)	2,100	22	3 (in A 1 hr. 45 min. and in B 1 hr. 38 min. after injection of 3 cc. of plain broth)	0:25 depression, urination; 0:32 respiration labored; 0:40 marked prostration; 0:55 general tremors; died next day	2,225	0:25 to 0:32 several successive rushes throughout small intestine—extremely violent reaction—heart became irregular; 0:35 death in asphyxial convulsions	Peristaltic rushes throughout small intestine
Salmonella sulpestifer	Topley (from Bruce White)	1,950	19	4	1:25 depression; 2:05 marked depression, 2:30 slight defecation, improved; moderate reaction	2,000	1:25 incomplete peristaltic rush in small intestine; 1:27 peristalsis in small intestine; 1:45 peristaltic rush in small segment of small intestine	Incomplete peristaltic rush in small intestine
	Tapoca (J. M. Research 43; 58, 1922)	1,310	17	3	0:50 depression; no other signs of reaction	1,810	Normal activity only observed.....	No definite excitation
Escherichia communior	1008 (a highly toxic organism furnished by Lister Institute)	1,850	18	4	0:40 marked distress, labored respiration, proceeding to complete collapse, which lasted for forty minutes. Recovered completely two days later	2,100	0:30 strong propulsion in lower colon; 1:35 considerable defecation—dyspnea slightly more marked at times—no definitely abnormal reactions of intestine observed	No definite excitation
	Blood (J. Exper. Med. 43: 448, 1926)	1,050	18	4	0:55 urination, prostration, labored respiration. Survived	2,250	During 2 hours, occasional mild pendulum movements in small intestine; lower colon spastic with occasional periods of activity	No definite excitation
Stock strain	Stock strain	1,050	20	3	0:58 severe diarrhea, rapid respiration, no prostration; 1:13 labored respiration. Survived	2,130	A change from the normal was not observed	No definite excitation



When the phenomenon occurred, it was induced by intravenous injection of a potent filtrate. Alvarez and Mahoney's<sup>4</sup> method was also different from ours. They immersed the animal in a saline bath and pinched the intestines by means of serrefines attached to heart levers. They themselves realized that this may have changed the gradient. We may further add from our own experience that considerable amounts of fluid are taken up by the tissues within a short



Fig. 3.—A spasm produced in a loop of small intestine during the passage of a peristaltic rush induced following the intravenous injection of a filtrate of a young culture of a strain of *Salmonella aëtrycke* (de Nobelet).

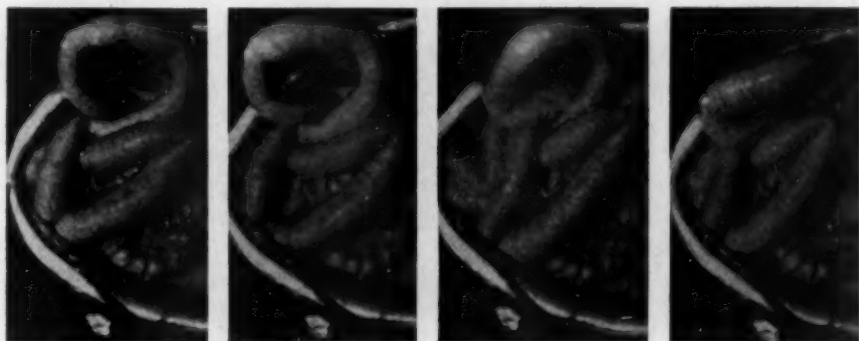


Fig. 4.—Serial enlargements of a 16 mm. moving picture film showing the passage of a peristaltic rush through part of a loop of small intestine, followed by relaxation. This reaction occurred following the injection of a filtrate of a young culture of a strain of *Salmonella enteritidis* (Deli Sumatra).

time when saline or Locke's solution is used, which should be considered as a factor in increasing the fluid content of the intestine.

It is evident that the most violent reactions occurred in those groups actually concerned in the production of acute gastro-intestinal disturbance, i. e., *Salmonella enteritidis* (Gärtner), *S. aëtrycke* and

TABLE 2.—The Production of Peristaltic Rushes in the Rabbit's Intestine with Filtrates of Young Cultures of the Colon-Typhoid Group of Organisms Correlated with the Generally Accepted Facts Concerning Disease Production by the Group (Modified After Snyder and Bosch)

	Salmonella paratyphi A (Brion and Kayser)	Salmonella enteritidis (Gärtner)	Salmonella schottmüller	Salmonella adirtryke	Salmonella suipestifer	Escherichia communior
Eberthella typhi Long incubation period; gradual onset; invades blood stream early	Much like typhoid, but may cause acute gastro-intestinal disturbance; invades blood stream early	Always causes acute gastro-intestinal disturbance; rarely invades the blood stream	Much like typhoid; invades the blood stream early; rarely produces acute gastro-intestinal disturbance	Always causes acute gastro-intestinal disturbance; rarely invades the blood stream	Much like typhoid, but may also produce acute gastro-intestinal disturbance; invades the blood stream	Common inhabitant of the intestinal tract of man and animals; occasionally invades the blood stream; doubtful whether it causes acute gastro-intestinal disturbance
Common in temperate zone and in tropics	More common in the tropics than in the temperate zone	Common in the temperate zone and in the tropics	More common in the temperate zone than in the tropics	Common in the temperate zone, not common in the tropics	Occasionally of importance in the temperate zone; endemic in Deli (Sumatra)	Ubiquitous
Disease of man	Disease of man	Disease of man and of animals associated with man	Disease of man	Disease of man and of animals associated with man	Disease of man and swine (monkey? cattle?)	May cause disease in man and animals
Not implicated in food poisoning	Usually not implicated in food poisoning	Causes food poisoning	Not implicated in food poisoning	Causes food poisoning	May cause food poisoning	Not implicated in food poisoning
Strains used did not produce a peristaltic rush	One of two strains used produced a peristaltic rush	All strains used produced peristaltic rushes	Strains used did not produce a peristaltic rush	All strains used produced peristaltic rushes	One of two strains used produced a peristaltic rush	Strains used did not produce a peristaltic rush

*S. suipestifer* (figs. 3 and 4). *S. paratyphi* A (Brion and Kayser) also produced marked reactions in the lower intestine. *Eberthella typhi*, *S. schottmülleri* and *Escherichia communior* showed little if any effect on the intestine.

Table 2 shows the correlation of these observations with the known clinical aspects of infection with the groups in man and animal, modified and enlarged from the arrangement by Snyders and Bosch.<sup>5</sup> From this table it is clear that the organisms that usually cause food poisoning affect both man and animal. The group includes mainly *S. enteritidis* (Gärtner), *S. aërtrycke* and *S. suipestifer*.

Some strains of *S. paratyphi* A (Brion and Kayser) may, under proper conditions, also produce the disturbance, but this subgroup usually is not implicated in the production of the disease. The first three forms, and particularly the first two, produce early in growth considerable amounts of diffusible toxic compounds. We have not seen evidence that the Schottmüller type of bacterium has been found associated with this condition.

One of us (Ecker) observed poor toxicity in filtrates of cultures of *S. aërtrycke* grown in Cole's<sup>6</sup> medium. The organisms which previously formed smooth colonies were changed to a rough type, and their filtrates were practically atoxic. Some 40 liters of filtrates were lost. Cole stated that in his tryptic digest broth, diphtheria bacilli also failed to produce a potent toxin. A few outbreaks of food poisoning have been produced by *S. suipestifer*. That it produces diffusible toxic substances in 2 per cent Witte peptone veal infusion broth was definitely demonstrated by Ecker and Richardson.<sup>7</sup> *S. suipestifer* is also, however, according to Snyders, the cause of a typhoid-like disease at Sumatra, Dutch East Indies, and may produce acute gastro-enteritis.

Correlating the capacity of a young culture filtrate to produce a peristaltic rush in the rabbit with the generally accepted clinical observations, we noted with interest that severe reactions in the intestine of the rabbit were induced only with filtrates from those organisms that are linked with the production of acute gastro-intestinal disturbance (food poisoning). So far as we are aware, ours was the first observation that peristaltic rushes directly follow injection of bacterial products.

It has been observed previously, and may also be noted in table 1, that diarrhea did not necessarily accompany the severe reactions which occurred following the injection of toxic filtrates. The absence of

5. Snyders, E. P., and Bosch, W. G.: Nederl. Tijdschr. v. Geneesk., vol. 4, 1928.

6. Cole, S. W.: Practical Physiological Chemistry, ed. 7, Cambridge, Eng., W. Heffer and Sons, 1926, p. 272.

7. Ecker, E. E., and Richardson, M. L.: J. Infect. Dis. 37:538, 1925.

diarrhea, however, may not be taken as evidence of the absence of intestinal reaction in the rabbit, as it was frequently observed that violent peristaltic rushes might fill the large saclike cecum with fluid while the greater part of the colon showed marked spasticity and prevented propulsion of the cecal contents beyond the upper part of the colon.

The method used in this study is being applied to other groups of intestinal organisms.

Of interest in this connection is the recent work of Koessler, Lewis and Walker,<sup>8</sup> who observed the effect of filtrates from bacterial growths in their study of pharmacologic action on arteries and bronchi. They found that, in a blood broth-glycerin-amino-acid medium, certain strains of many common pathogenic micro-organisms—pneumococci, streptococci, *Bacillus coli*, *B. typhosus* and *B. paratyphosus*—formed substances which caused arterial constriction in vitro and bronchial constriction in the living guinea-pig. They asserted that the action of the poisons was frequently selective. They also stated that filtrates that caused bronchiolar constriction sometimes did not have any action on the smooth musculature of the arteries, and vice versa. A spasm of both bronchi and arteries was, however, frequently obtained with the same filtrate. They claimed that in the majority of cases they dealt with poisons of unknown chemical constitution.

#### SUMMARY

A new method was devised for the observation and recording by motion pictures of intestinal motility in rabbits. The method was applied to the study of the colon-typhoid group of organisms, with particular reference to the effect of filtrates of young cultures on the intestines. The young culture filtrates of certain subgroups of the colon-typhoid group were found to produce violent intestinal reactions (peristaltic rushes and circular muscle spasms). The culture filtrates of those organisms commonly known as producers of food poisoning and which cause violent acute intestinal reaction in man (*S. enteritidis*, *S. aertrycke* and *S. suipestifer*) were found to be the ones which induced peristaltic rushes in rabbits; while culture filtrates of other organisms of the group, which may at times have been implicated in outbreaks of food poisoning (for example, *S. paratyphi* A) were variable in their effect. Some filtrates of organisms not definitely known to be associated with outbreaks of food poisoning (*Eberthella typhi*, *Escharichia communior* and *S. schottmülleri*) failed to produce a visible effect. It was further observed that the most effective filtrates were obtained from cultures of those types that cause disease in both man and animal (*S. enteritidis*, *S. aertrycke* and *S. spipestifer*).

8. Koessler, K. K., and Lewis, J. H.: Determination of Bronchospasm in the Guinea-Pig. Arch. Int. Med. **39**:163 (Feb.) 1927.

## THE CIRCULATION OF BLOOD THROUGH THE SPLEEN PULP\*

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### THE BLOOD VESSELS OF THE SPLENIC LOBULE

In April, 1926, at the Albany Session of the Association of American Pathologists and Bacteriologists, sections of the spleen from human beings and from rabbits were demonstrated, showing in an apparently convincing manner the termination of arterial capillaries by opening out into the intercellular spaces of the spleen pulp of the marginal zone about the follicle.<sup>1</sup> Further studies have fully confirmed these observations and have led to the recognition of an anatomic unit of spleen structure outlined by the most widely distended venous capillaries in the distended spleen, and this structural unit has been designated as the splenic lobule.<sup>2</sup>

The central portion of the lobule is occupied by the malpighian corpuscle or splenic follicle. Around this is the marginal zone or intermediate zone of the lobule, characterized by the presence of small arterial capillaries in a close meshwork of reticulum and pulp cells and by remarkable freedom from venous capillaries. Peripheral to this zone, the pulp cords extend to the periphery of the lobule, separated from each other by venous capillaries or sinuses, which are largest at the border of the lobule.

The continuation of these studies, as opportunities have occurred, permits the presentation of some further evidence and may, perhaps, warrant the enunciation of certain conceptions in regard to the splenic circulation of man, which have heretofore been rather indefinite.

The follicle itself is provided with a rich supply of thin-walled capillary vessels given off from the follicular artery or its branches and anastomosing within the follicle and at its periphery. These capillary vessels finally terminate by short twigs which extend into the marginal

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\* From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

1. MacNeal, W. J.: The Open Circulation of the Spleen Pulp, *Am. J. Path.* **2**:473, 1926. MacNeal, W. J.; Otani, Sadao, and Patterson, Marjorie, B.: The Finer Vascular Channels of the Spleen, *ibid.* **3**:111, 1927.

2. MacNeal, W. J.: The Splenic Lobule, *Contributions to Medical Science Dedicated to Aldred Scott Warthin*, Ann Arbor, George Wahr, 1927, p. 525; abstr., *Arch. Path.* **3**:565 (March) 1927.



zone and there become continuous with the intercellular spaces of the spleen pulp in this region. Under normal circumstances, therefore, these vessels permit the passage of plasma through their walls to bathe the structures of the follicle, but retain the formed elements of the blood and discharge them into the meshes of the marginal pulp. Within the follicle the pulp spaces are free from erythrocytes.

#### TYPES OF ARTERIAL CAPILLARIES

The marginal zone presents a sharp contrast to the follicle. Here there are abundant erythrocytes in the intercellular spaces of the pulp. In the spleen distended by perfusion, the marginal zone is seen to be free from venous capillaries. Arterial capillaries, however, are abundant here. They are of two kinds.

In the first class are those which represent terminations of the follicular capillaries. These are extremely narrow, and their walls consist of a single layer of thin endothelium. Some of them extend only a minute distance from the follicle before opening out into the pulp. This type was illustrated, not too clearly, by the photomicrograph, figure 2 of plate 42 in volume 3 of the *American Journal of Pathology* (1927) and by the drawing of the same structure shown in figure 13 of plate 48 in the same publication.<sup>1</sup> A similar capillary termination is shown in figure 1 of the present paper. The lumen of the capillary can be traced through the capsule of the follicle to become somewhat distended and then continuous with the intercellular spaces of the pulp reticulum. Sometimes it is possible to trace these follicular capillaries for a longer distance into the marginal zone, as is shown in figures 2 and 3, but they always terminate in the pulp at a considerable distance from the nearest venous capillary. In the human spleen, the termination is usually asymmetrical, so that the opening appears larger toward one side. The rod-shaped endothelial cells of the capillary wall become continuous with the reticular cells of the pulp. Sometimes their cytoplasm is spread out into a broad thin sheet at one side of the termination, as is shown in figure 3. The distended tip or terminal ampulla attains a diameter of only 10 to 15 microns in the preparations and is quite short. Sometimes it is possible to trace a follicular capillary to the marginal zone only to arrive at a blind end as the capillary walls come together (fig. 4). Erythrocytes are often found in the patent lumen of such a vessel. Evidently, these follicular capillaries function in an intermittent manner, as is known to be true of the cutaneous capillaries (Krogh<sup>2</sup>) and of the

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3. Krogh, August: The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation, *J. Physiol.* **52**:457, 1918-1919; Studies on the Capillariomotor Mechanism, *ibid.* **53**:399, 1919-1920; Studies on the Physiology of Capillaries, *ibid.* **55**:412, 1921.



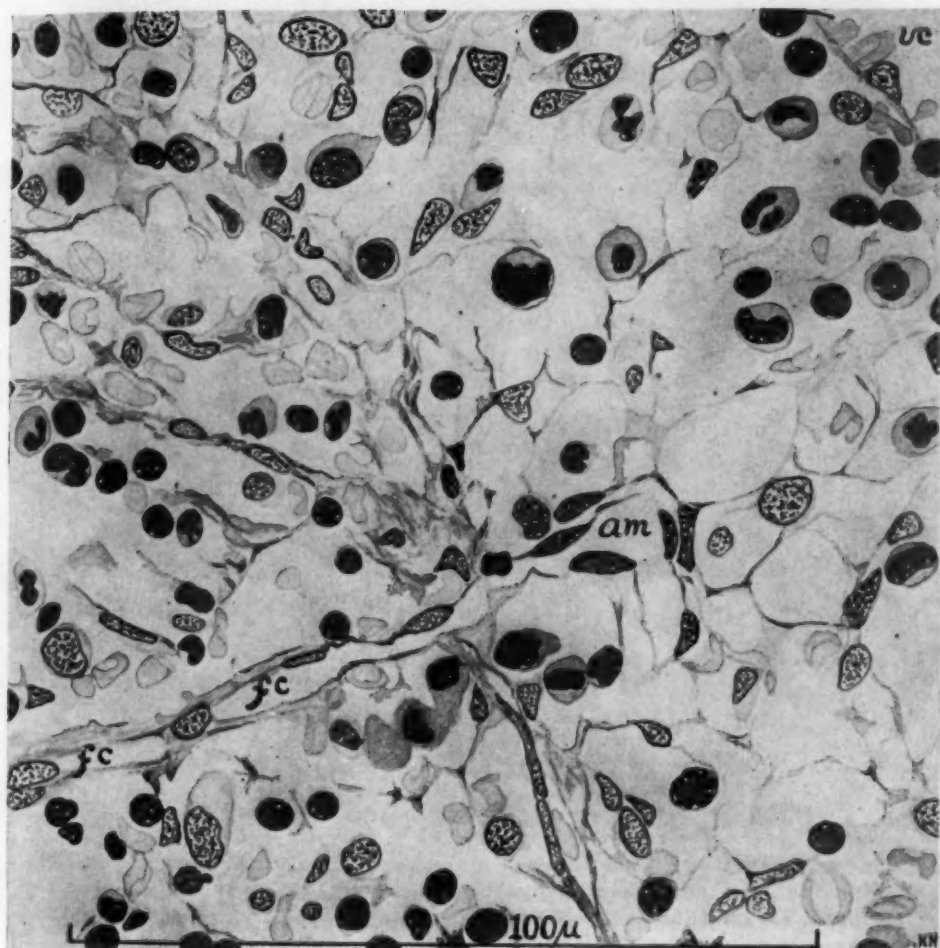


Fig. 1.—Spleen from a human being; termination of a follicular capillary in the marginal zone. The follicular capillary (*fc*) passes upward and to the right going through the capsule of the follicle slightly below the center of the figure to terminate in a slightly distended ampulla (*am*) in the pulp of the marginal zone. Here its lumen becomes continuous with the intercellular spaces of the pulp. The nearest venous capillary (*vc*) is seen at the upper right corner. The spleen was perfused three hours postmortem. It was the spleen of a boy, aged 8 months, who died of gangrenous inflammation of the mouth, pharynx and esophagus. Camera lucida drawing by Dr. Kiyoshi Hosoi.

capillary tufts of the renal glomeruli (Richards<sup>4</sup>). In one vessel, the perfusion fluid is allowed to pass and distend the terminal portion as an ampulla, while another capillary remains collapsed at its tip or even for a large part of its course.

The second kind of arterial capillary in the marginal zone is the centripetal capillary given off from the sheathed arterioles of the red pulp. According to my observations up to the present, these sheathed arterioles are branches of the vessel which continues as the eccentric arteriole of its respective follicle. I was unable to confirm the observation of Hueck,<sup>5</sup> who found by reconstruction studies that sheathed

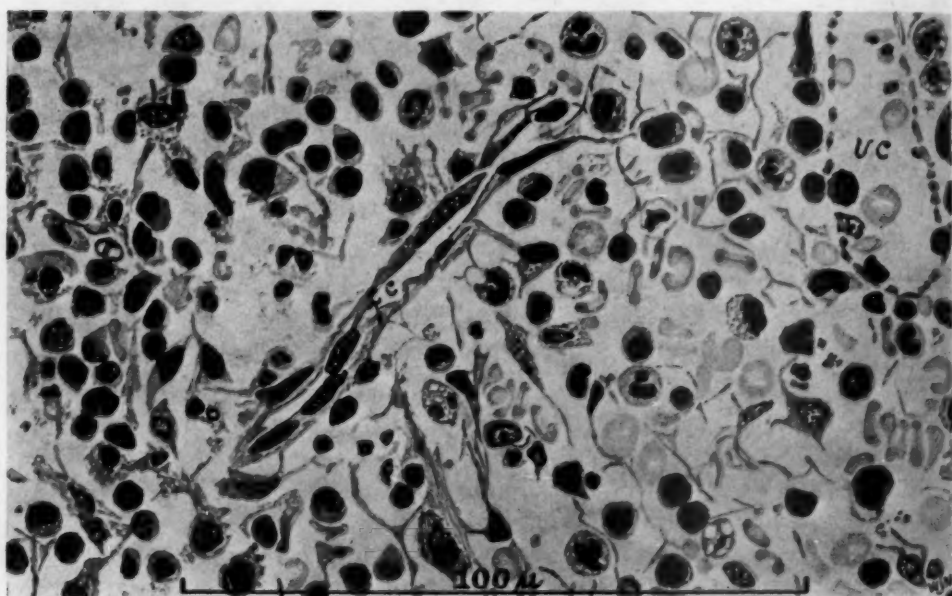


Fig. 2.—Spleen from a human being; termination of a follicular capillary in the marginal zone. The follicle is at the left. The follicular capillary (*fc*) passes upward and to the right to open out into the intercellular spaces of the pulp near the top of the picture. The nearest venous capillary (*vc*) is seen at the upper right corner. The spleen was removed at operation on a boy aged 7 years, with anemia, chronic purpura and thrombocytopenia. It was perfused immediately after removal.

arterioles coming from eccentric arteries of other follicles are present in the marginal zone. These centripetal capillaries come out of the ellipsoids of Schweigger-Seidel as narrow vessels with extremely thin

4. Richards, A. N.: The Nature and Mode of Regulation of Glomerular Function, *Am. J. M. Sc.* **170**:781, 1925.

5. Hueck, W.: Ueber den Bau der Lymphknoetchen der Milz, *Verhandl. d. deutsch. path. Gesellsch.* **22**:238, 1927.

walls. Such a capillary usually branches quickly into two terminal twigs, which are directed obliquely toward the follicle and terminate in small ampullar dilatations which open out into the intercellular spaces of the pulp (figure 5). This type of termination was pictured in figures 4 and 14 of an earlier paper.<sup>1</sup> The present example is from another spleen in which the perfusion and fixation were more satisfactory. In the spleen of the rabbit, some of these centripetal capillaries appear to anastomose with the follicular capillary plexus. In the spleens of human beings, such connections have so far escaped my observation.

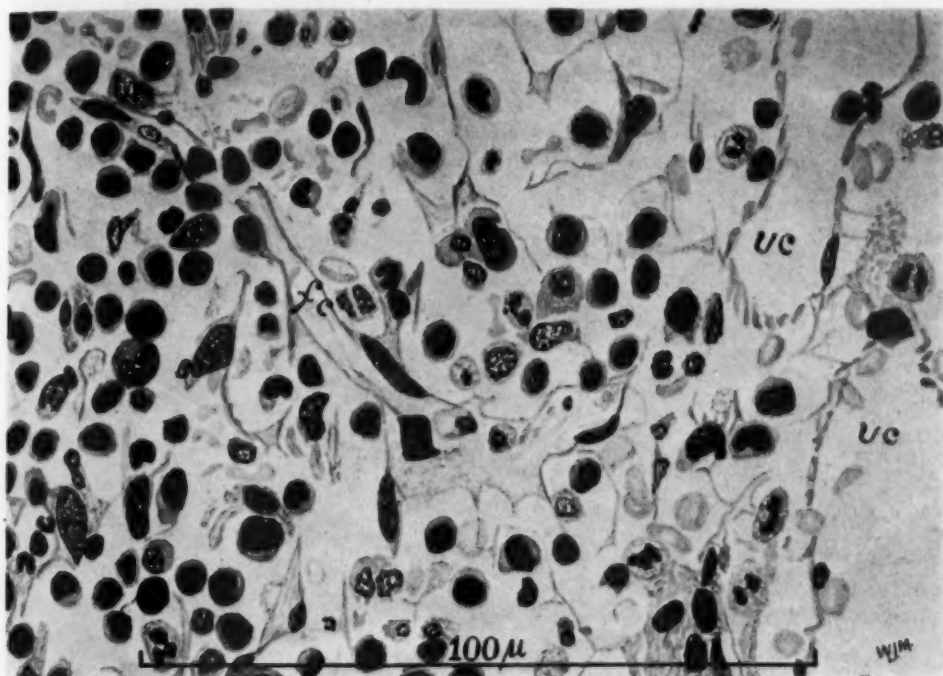


Fig. 3.—Spleen from a human being; termination of a follicular capillary in the marginal zone. The follicle is at the left of the drawing. The capillary (*fc*) terminates in the pulp just below the middle of the picture, and the nearest venous capillaries (*vc*) are seen at the right extending to the upper and lower corners of the drawing. Same spleen as in figure 2.

The third variety of arterial capillary of the human spleen is the arterial capillary of the pulp cord. This arises from a sheathed arteriole, as does the capillary just described. The same sheathed arteriole may give rise to several capillaries of both these varieties. The capillary of the pulp cord is longer than the others. It sometimes is quite straight, but often curves through the arc of a circle. For most of its course, it

lies well within a pulp cord, with a distinct layer of pulp reticulum between it and the nearest venous sinuses. At times, however, the capillary wall lies in contact with that of a venous sinus, and one may easily mistake such a contact for actual communication, if the section is thick and otherwise misleading. In thin serial sections, the arterial vessel will be found to pass along without opening into the venous sinus in its course. It may give off short lateral twigs which quickly terminate in the pulp reticulum. The main capillary terminates in a slightly distended irregularly asymmetrical ampulla which is situated in the midst

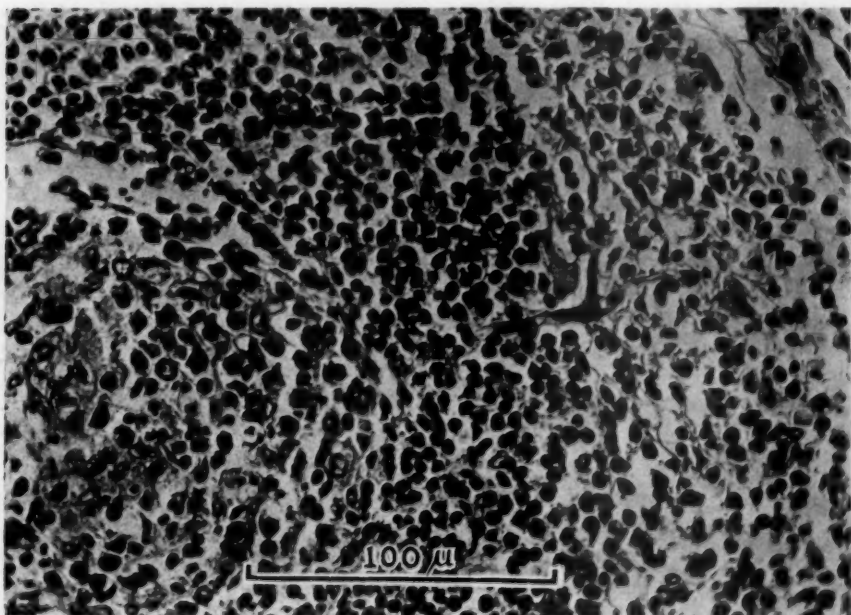


Fig. 4.—Photomicrograph of spleen from a human being. A follicular capillary is seen at the right of the center, running toward the right. This vessel is collapsed in part and could not be traced any farther in the adjacent sections of the series. The spleen was perfused two hours after death following a tonsillectomy in a well developed boy, aged 4 years. The measurement line represents 100 microns.

of a pulp cord as far as possible from the nearest venous sinuses (fig. 6). An arterial capillary of this type was illustrated by figures 9 and 15 of an earlier paper.<sup>1</sup> Such capillaries are more easily recognized than the shorter ones previously discussed. They tend to run in a rather straight course, especially near the external capsule of the spleen, as has been pointed out by Neubert.<sup>6</sup>

6. Neubert, Kurt: Der Uebergang der arteriellen in die venose Blutbahn bei der Milz, *Ztschr. f. ges. Anat. u. Entwicklungsgesch.* 66:424, 1922.



Although the rabbit's spleen is much like that of man, there are distinct differences in the arterial capillaries. For example, in the long capillary of the pulp cord, the termination in the rabbit's spleen is a much more symmetrical and more definitely demarcated terminal ampulla, with a wall made up of many distinctly rod-shaped endothelial cells with large, oval, brightly staining nuclei. One of these is illustrated in figure 7. Here the plane of section has included the axis of the terminal portion of the vessel for a considerable stretch.

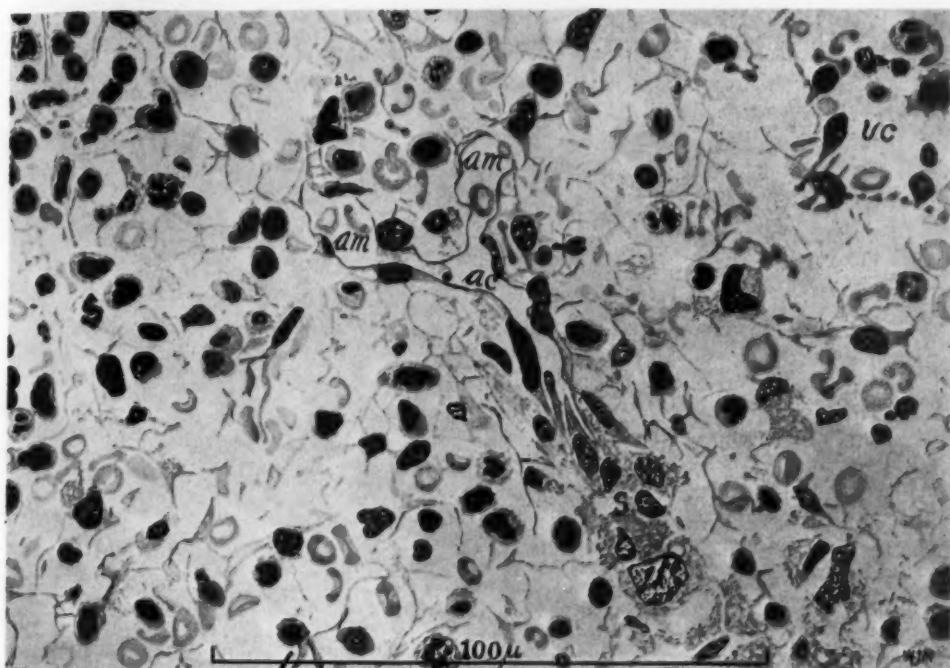


Fig. 5.—Spleen from a human being; centripetal arterial capillary of the marginal zone. The capillary (*ac*) extends upward and to the left from the lower margin of the drawing, the thick wall, constituting the sheath of Schweigger-Seidel (*s*), being cut at one side of the lumen. The lumen appears near the center of the drawing, and the sheath becomes indistinct and disappears. Near the termination, the thin-walled capillary divides, and the two branches become distended into ampullae (*am*), which open out into the intercellular spaces of the pulp of the marginal zone. The follicle is at the upper left corner of the drawing, its margin just appearing there. The nearest venous capillary (*vc*) is at the upper right margin of the drawing. Same spleen as that in figure 2.

The arterial ampullae of the spleen in man and of the rabbit's spleen here described and pictured are regarded as identical with the ampullae



described by Golz<sup>7</sup> and Thoma.<sup>8</sup> It is not so easy to identify them with the funnel-form ampullae described and pictured by Neubert<sup>6</sup> for the spleens of cats, swine and dogs. One is in some doubt whether the prolonged perfusion (from three to five hours) employed by Neubert may not have resulted in the rather extensive disintegration of the walls of the capillary terminations and thus have produced large spaces in the pulp surrounded by pulp reticulum. My observations on the spleens of the animals used by Neubert are still too limited to warrant a final opinion on this question.

#### THE VENOUS SYSTEM

The intercellular spaces of the pulp reticulum constitute the essential pathway through which the blood must pass from the terminations of

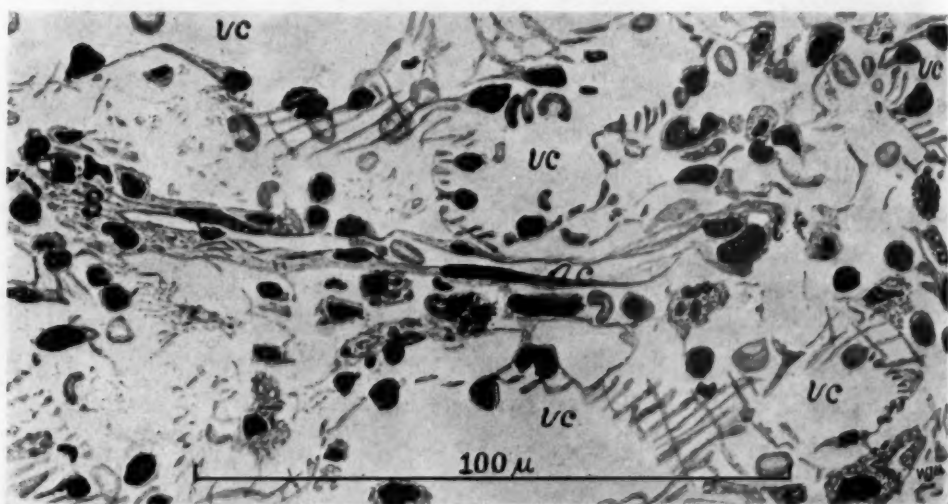


Fig. 6.—Spleen from a human being; arterial capillary of the pulp cord. The capillary (*ac*) extends from the left border almost to the right border of the picture. At either side of it are venous capillaries with fenestrated walls. The termination of the arterial capillary (*t*) is almost equally distant from three venous capillaries (*vc*). At the left, the arterial capillary has a thick sheath (*s*). Same spleen as that of figure 2.

the arterial capillaries to reach the first vessels of the venous system. This statement conforms to the view of those who have, for almost a century, maintained that the splenic circulation is an open circulation.

7. Golz, Sigismund: Untersuchungen über die Blutefässe der Milz, Inaug. Diss., Jurjew, 1893.

8. Thoma, R.: Ueber die Blutefässe der Milz, Arch. f. Anat. u. Entw.-Ingsgesch., 1899, p. 267; Die normale Blutstrom und die venöse Stauung in der Milz, Virchows Arch. f. path. Anat. **249**:100, 1924.

The experimental demonstration of the immediate passage into pulp spaces of the spleen, of the erythrocytes of birds introduced into a short gastric branch of the splenic artery of a living rabbit, reported in March, 1926,<sup>9</sup> has brought strong support to this conception, to which there no longer appears to be any active opposition. Morphologic observations on serial sections may, therefore, now be more confidently employed to supply the detailed information in regard to this pathway. In the marginal zone, the direct opening of the terminal ampullae into the pulp spaces is easily seen and is distinctly shown in figures 1, 2, 3 and 5. In the arterial capillaries of the pulp cords, the openings into the pulp spaces appear somewhat smaller and are seen as openings in the wall of the ampulla between the endothelial cells, more irregularly arranged in man than in the rabbit. Blood cells are occasionally caught in transit from the arterial capillary to the pulp space. Everywhere in



Fig. 7.—Spleen of a rabbit; terminal ampulla of an arterial capillary of the pulp cord. The ampulla surrounded by pulp reticulum is shown at the center of the drawing. The nearest venous capillary (*vc*) is at the extreme upper left corner of the drawing. Section of a spleen perfused and fixed in the living animal.

the intercellular spaces of the red pulp one finds erythrocytes and other blood cells in intimate relation to the reticular cells of the pulp. It is here that phagocytosis of the blood cells is most abundant. Undoubtedly, the rate of passage is slow in these spaces and it is influenced not only by the arterial pressure but also by the contraction of muscle in the splenic capsule and trabeculae, and probably also by the contraction of the reticular cells and of the rod cells lining the venous sinuses, as has been suggested by Neubert<sup>6</sup> and by Foot.<sup>10</sup> From the pulp spaces, the

9. MacNeal, W. J., and Patterson, Marjorie, B.: The Pathway of Nucleated Erythrocytes Introduced into the Splenic Artery, *Proc. Soc. Exper. Biol. & Med.* **23**:420 (March 17) 1926.

10. Foot, N. C.: The Reticulum of the Human Spleen, *Anat. Rec.* **36**:79 (July) 1927.

blood escapes into the venous sinuses through the fenestrations in the walls of the latter, the stomas of Mollier. These openings are easily recognized in any thin section of a well perfused spleen. They are illustrated in figures 2, 3, 6 and 8.

The venous system proper begins in a plexus of richly anastomosing channels, everywhere running between the pulp cords throughout the peripheral portions of the lobules. These channels are the venous sinuses. They are illustrated particularly in figures 6 and 8. Their walls are composed of rod-shaped endothelial cells with large oval nuclei that project into the lumen. These cells are sometimes attached to each other by protoplasmic processes but, in general, they are separated by parallel longitudinal clefts, which are crossed at intervals by slender

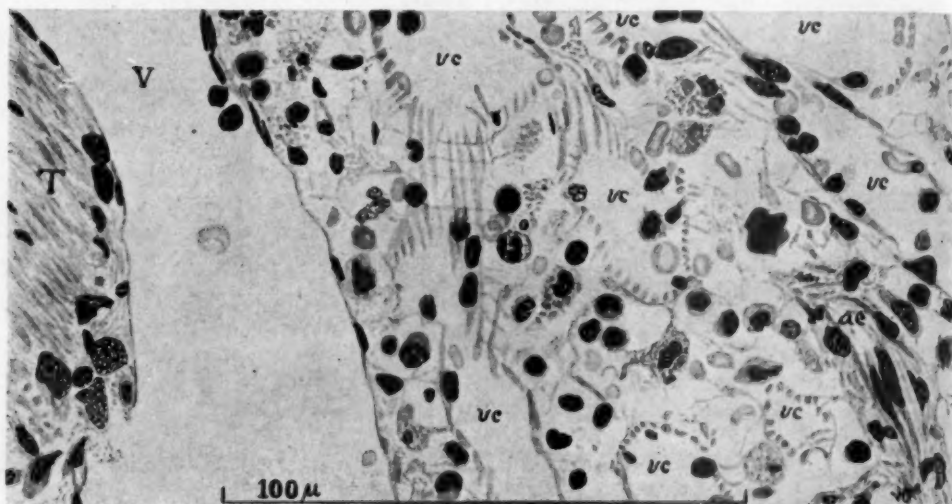


Fig. 8.—Spleen from a human being; pulp near the periphery of the lobule. Near the middle of the drawing one recognizes the venous capillaries (*vc*) of the pulp with their fenestrated walls lined by the rodlike endothelial cells, which have oval nuclei projecting into the lumen. To the left is seen a trabecula (*T*) and a larger vein (*V*), which is lined by a continuous layer of endothelium, the cells of which are flattened and contain flattened nuclei. An arterial capillary (*ac*) appears at the right lower corner of the drawing. Same spleen as that in figure 2.

reticular strands external to the rod cells and continuous with the pulp reticulum. The diagrammatic figure of Mollier, which has been so extensively copied, appears essentially correct. However, it should be noted that the caliber of a sinus is never the same for any considerable distance and that its course is tortuous, so that the diagram of a straight cylinder of even diameter may mislead the uninitiated. The sinus shown passing in a vertical direction in the middle of figure 8 is typical for the human spleen. This system of anastomosing sinuses opens widely near

the periphery of the lobule into small splenic veins, interlobular veins, which are lined by a continuous sheet of thin endothelial cells with flattened nuclei, distinctly different in form from the endothelial cells which form the walls of the sinuses. These veins come into relation with one of the trabeculae of the capsule, at first on one side, and later empty into the trabecular veins which lie within the substance of the trabeculae (fig. 8).

#### PHYSIOLOGIC SIGNIFICANCE

The anastomosing network of fine thin-walled capillaries within the substance of the follicle is often entirely collapsed and blood-free in microscopic sections of undistended spleen. In the perfused spleen, these vessels may contain only cell-free fluid, although erythrocytes are occasionally seen in them. Hueck<sup>5</sup> thought that these minute vessels carry chiefly plasma. However, they come off rather directly from the eccentric arteriole or short intermediate branches of it. I am convinced that they carry blood, but that they tend to become empty rapidly with the fall of arterial pressure at death, by their own elasticity and because of the pressure of the surrounding follicular substance, which, during life, is distended by the arterial pressure in its interior. This capillary plexus provides a rich nutrition for the follicle. Through the thin capillary walls, the plasma evidently passes in considerable amount to the intercellular spaces of the follicle, coming into immediate contact with the reticular cells and with the proliferating lymphocytes. Toxic substances dissolved in the plasma are thus brought into intimate relationship with lymphatic cells, under conditions favorable for the chemical action of these cells.

The formed elements of the blood remain within the capillary lumen until they have reached the periphery of the follicle. There they pass through the open capillary ampullae directly into the intercellular pulp spaces of the marginal zone. Here is afforded an opportunity for a most effective testing of these formed elements. The contraction and dilatation of the pulp meshes subject them to physical pressure and distortion, as has been pointed out by Schmincke<sup>11</sup> and by Neubert.<sup>6</sup> Slowing of the current favors agglutination, and the intimate contact with the pulp cells permits phagocytosis of those formed elements destined for destruction.

The centripetal capillaries of the marginal zone furnish a rich nutritional blood supply to the periphery of the follicle, and they also discharge their formed elements into the intercellular spaces of the marginal zone. It is at once evident that this marginal zone about the follicle is

11. Schmincke, A.: Ueber die normale und pathologische Physiologie der Milz, München. med. Wchnschr. 63: (July 11) 1005, (July 18) 1047, (July 25) 1083, (Aug. 1) 1118, 1916.



the most important part of the lobule, as far as action on formed elements in the blood is concerned. Here phagocytosis of worn out blood cells and of foreign matter, such as microbes, occurs most abundantly.

In man, the centripetal capillaries come from arterial twigs enclosed in the ellipsoidal sheaths of Schweigger-Seidel. The physiologic significance of these curious sheath structures appears not to be fully elucidated. They doubtless have something to do with regulating the lumen of the arterial vessel in the interior, and thus regulate the relative amount of blood which may be delivered to the centripetal capillaries and the long capillaries of the pulp cords, as against the amount going to the intra-follicular capillary plexus, which is derived from arterioles without ellipsoid sheaths. The purpose subserved by such a regulation is not clearly revealed. Furthermore, it is not clear whether this mechanism is merely a local adaptation, whether it may be influenced by substances in the blood, such as hormones or drugs, or whether it is subject to nervous control. In the literature, one finds the suggestion that the ellipsoids serve as valves to prevent the reflux of blood from the pulp spaces into the arterial circulation. Assuming that the pressure within the pulp spaces might become greater than that within the arterial capillaries, it is nevertheless evident that all the splenic capillaries tend to collapse completely unless they are kept distended by arterial pressure greater than the pressure around them. One does not, therefore, need to recognize a special valvular action of the ellipsoids to explain the impossibility of perfusing a spleen in the reverse direction. I am not inclined to recognize this as a special function of the ellipsoids. The suggestion that the ellipsoids permit the passage of plasma through their substance and thus act chemically on dissolved substances in the fluid portion of the blood, somewhat as the follicles probably do, seems worthy of consideration. Adequate proof of this suggestion is lacking. Another possibility, which appears worthy of consideration, is suggested by the resemblance of the ellipsoid sheaths to the tissue of the follicles in the rabbit's spleen. Possibly the ellipsoids may be embryonic structures, capable of development into follicles as occasion may demand. A study of perfused fetal spleens might elucidate this point.

The long capillaries of the pulp cords terminate near the periphery of the lobule, with a thin layer of pulp between their terminations and the venous sinuses. Such an arrangement suggests that the blood cells passing through them escape into the veins without being subjected to much action of the spleen substance. These vessels are so long and slender, and their terminations are so far removed from the larger arteries, that any increase in pressure within the pulp, whether by passive congestion or by active contraction of the spleen, should result in their occlusion, thus forcing relatively more blood into the marginal zone about



the follicle. On the other hand, relaxation of the splenic musculature and low venous pressure would favor the passage of abundant blood through these longer capillaries, so that relatively more blood would escape the action of the splenic pulp of the follicle and of the marginal zone. Suggestions of this sort challenge experimental investigation. They may be of some significance in explaining pathologic changes in the structure of the spleen and especially in the localization of the parasitic microbes.

#### SUMMARY

1. It is possible to recognize a definite splenic lobule consisting of malpighian corpuscle, its marginal zone and the radiating pulp cords with the included vessels. The periphery of the lobule is marked by the widest venous sinuses in the distended spleen.

2. The arterial blood vessels of each lobule are terminal, without anastomosis with arterial vessels of other lobules. There are three kinds of capillaries: (1) the anastomosing capillary plexus of the follicle, which arises from the eccentric arteriole or a branch of it; (2) the centripetal capillaries of the marginal zone, which arise from a sheathed branch of the intralobular artery; (3) the long capillaries of the pulp cords, which arise from the same sheathed arteriolar branches.

3. The arterial capillaries of the follicle and the centripetal capillaries open out into the intercellular pulp spaces of the marginal zone at considerable distances from the nearest venous sinuses. The arterial capillaries of the pulp cords terminate in more or less well defined ampullae within the substance of a pulp cord, but separated from the adjacent venous sinuses by a thin layer of the pulp.

4. Apparently, the arterial capillaries are patent only part of the time during life and all tend to collapse entirely at death. Perfusion and fixation in the distended state is essential in order to show the natural form and size of these vessels.

5. The anatomic arrangement of the spleen permits a partial separation of the blood plasma from the formed elements of the blood. The plasma comes into intimate relation with the lymphatic elements of the follicles, while the corpuscular elements come into immediate contact with the reticular cells of the red pulp. These relations appear to be of physiologic significance.

6. The venous system begins in a plexus of richly anastomosing sinuses found everywhere between the pulp cords in the peripheral portion of the lobule. They have fenestrated walls which permit the entrance of elements of the blood from the reticular spaces of the pulp.

## CHROMAFFIN CELL TUMOR OF THE SUPRARENAL MEDULLA (PHEOCHROMOCYTOMA) \*

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The chromaffin system as a tissue system was established by Kohn.<sup>1</sup> He based his conclusion that chromaffin tissues constitute a definite entity on the following facts, which apply wherever the tissues are found:

1. They have a common embryonic origin—the anlage of the sympathetic ganglions—in both phylogenetic and ontogenetic development.
2. They give a characteristic reaction to chromic salts (Henle).<sup>2</sup>
3. Extracts of these tissues possess the biologic property of causing a rise in blood pressure and glycosuria when inoculated into animals.
4. They are indispensable in the maintenance of life.

Tumors of this tissue are rare. They are of considerable interest. In their structure and location they bear out some of the facts that have been learned concerning the chromaffin system from which they arise. The possibility is presented that they are actively secreting tumors of an organ of internal secretion, the prolonged absorption of the secretion of which by the body causes the exaggerated biologic effects that are associated with these tumors.

It is for these reasons that this case is here reported; and since up to this time there has not been any systematic collection of cases of tumors of the chromaffin cells of the suprarenal medulla, all the available information concerning the reported cases, thirty in number, has been summarized, and a critical review of the many beliefs held in relation to certain aspects of their histologic constitution and associated clinical conditions has been added.

### EMBRYOLOGIC CONSIDERATIONS

For the better appreciation of the constitution and biologic aspects of these tumors, it would be well to recall certain facts concerning the development of the tissue from which they arise. The suprarenal cortex develops from the splanchnic mesoderm. Developmentally, and in most respects functionally, also, it may be considered a separate organ; it

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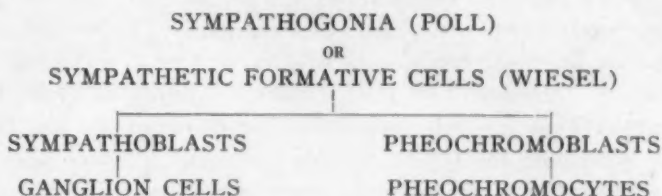
\* Submitted for publication, Sept. 17, 1928.

\* From the Laboratories of the Mount Sinai Hospital.

1. Kohn, A.: Paraganglien, Arch. f. mikr. Anat. u. Entwicklgs. **62**:263, 1903.

2. Henle, J.: Ueber das Gewebe der Nebenniere und der Hypophyse, Ztschr. f. rationelle Med. **24**:143, 1865.

does not concern the present study.<sup>3</sup> The immediate anlage of the suprarenal medulla, and the anlages of the remainder of the chromaffin organs, lie in the sympathetic ganglions, which, in turn, are derived from the cells of the neural crest. In the human 17 mm. embryo may be seen the beginning of the migration of the primitive cells of these ganglions, the sympathogonia, or the sympathetic formative cells, laterally. This migration continues during early fetal life. In mammals, the sympathogonia migrate until they reach the cortical anlage of the suprarenal gland. In the selachians, the migration ends just lateral to the aorta. Migration is complete in the 85 mm. embryo; at this time, they have taken up the position of the medulla.<sup>4</sup> During the migration, portions of the embryonic tissue may become split off; these develop as separate organs at varying distances from the aorta in the region of the renal arteries or the inferior mesenteric artery to form the organs of Zuckerkandl.<sup>5</sup> The further development of the suprarenal medulla consists in the process of differentiation from sympathogonia to the mature elements. This may best be diagrammatically plotted:<sup>6</sup>



This process of differentiation takes place in the last months of fetal life, and, according to Wiesel, is not completed until about the time of puberty.<sup>7</sup> The sympathogonia, the parent cells of the sympathetic and pheochromic systems, are small round cells, slightly larger than lymphocytes, with each a scanty cytoplasm and a round, large nucleus containing a densely staining chromatin network. These differentiate on the pheochromic side into larger cells, also round, with each a larger area of clear cytoplasm and a more vesicular nucleus. The final stage of differentiation brings forth the mature pheochromocytes, which are large,

3. Kohn, A.: Ueber die Nebenniere, *Prag. med. Wchnschr.* **23**:193, 1898.

4. Wiesel, J.: Beiträge zur Anatomie und Entwicklungsgeschichte der menschlichen Nebenniere, *Anat. Hefte* **19**:481, 1902.

5. Zuckerkandl, E.: Ueber Nebenorgane des Sympathikus im Retroperitonealraum des Menschen, *Verhandl. d. anat. Gesellsch.* **15**:95, 1901.

6. Poll, H.: Die vergleichende Entwicklung der Nebennierensysteme, in Hertwig: *Handbuch der Entwicklungsgeschichte der Wirbeltiere*, Jena, Gustav Fischer, 1906, vol. 3, p. 442.

7. Wiesel, J.: Bemerkungen zu der Arbeit H. Kusters "Ueber Gliome der Nebennieren," *Virchows Arch. f. path. Anat.* **180**:553, 1905.

irregular or polyhedral cells, with each a round or ovoid vesicular nucleus, containing a loose chromatin network, and a well formed nucleolus. The cytoplasm is abundant and usually finely granular. In contradistinction to the pheochromoblasts, the pheochromocytes have the peculiar property of staining brown with chromic salts. It is the abnormal proliferation of these mature cells that makes up the tumor of the suprarenal medulla variously known as chromaffin tumor, paraganglioma or pheochromocytoma. The other groups of tumors arising from the suprarenal medulla, the neuroblastomas and ganglioneuromas, are derived from cells developing along the other line, comprising the nervous or nonspecific elements of the suprarenal glands.

#### REVIEW OF THE LITERATURE

The first report of a medullary tumor of the suprarenal gland that may be considered a pheochromocytoma was that of Berdez in 1892, who described a vascular, encapsulated tumor within the medulla of the right suprarenal gland.<sup>8</sup> Like most of the tumors reported subsequently, it did not replace the entire medulla, but was demarcated from the remaining normal medullary tissue. Two years previously, Perley<sup>9</sup> had reported such a tumor, but his description of it is too meager to make one certain of its nature. Manasse,<sup>10</sup> in 1893, reported a tumor observed by him three years previously which showed the characteristics of a pheochromocytoma. He found the typical hyaline inclusions that one sees in the normal suprarenal medulla, noticed some cells that he considered as probably ganglion cells and also noted tumor cells in the suprarenal veins. Three years later, he reported a second case in which he demonstrated the chromaffinity of the cells composing the tumor.<sup>11</sup> Marchetti<sup>12</sup> was the first to describe a bilateral pheochromocytoma of the suprarenal medulla, in 1904. Suzucki,<sup>13</sup> in 1909 and 1910, reported three cases, one of which was necrotic and cystic. His was the first case reported as occurring in conjunction with neurofibromatosis. He also noted the pres-

• 8. Berdez: Contribution a l'étude des tumeurs des capsules surrénales, Arch. d. méd. expér. et d'anat. path. **4**:414, 1892.

• 9. Perley, cited by Herxheimer: Beitr. z. path. Anat. u. z. allg. Path. **57**:115, 1914.

• 10. Manasse, P.: Ueber die hyperplastischen Tumoren der Nebennieren, Virchows Arch. f. path. Anat. **133**:391, 1893.

• 11. Manasse, P.: Zur Histologie und Histogenese der primären Nierengeschwülste, Virchows Arch. f. path. Anat. **145**:127, 1896.

• 12. Marchetti, G.: Beitrag zur Kenntnis der pathologischen Anatomie der Nebennieren, Virchows Arch. f. path. Anat. **177**:227, 1904.

• 13. Suzucki, S.: Ueber zwei Tumoren aus Nebennierenmarkgewebe, Berl. klin. Wehnschr. **47**:1623, 1910; Ueber einen chromaffinen Tumor des Nebennierenmarks, ibid. **46**: 1644, 1909.



ence of sympathetic formative cells. Laignel-Lavastine and Aubertin<sup>14</sup> in the same year noted the occurrence of melanoderma in their cases. Neusser and Wiesel,<sup>15</sup> in 1910, reported the unusual occurrence of this tumor in a 2 year old child, who had the vascular changes of an epinephrine sclerosis, and at the same time they included a case of Kolisko's, the first in which signs of vasomotor instability were noted. Herde,<sup>16</sup> in discussing two cases of his, considered the tumors to be hamartomas in the sense of Albrecht.<sup>17</sup> In 1913, Helly<sup>18</sup> reported a case with hypertension and glycosuria without renal or pancreatic disease. A year later, Hedinger<sup>19</sup> reported a case associated with cystic degeneration and suggested the name *struma medullaris cystica suprarenalis*. Harbitz,<sup>20</sup> in 1915, reported a chromaffin cell tumor of the suprarenal gland as occurring in conjunction with a hypernephroma. L'abbé, Tinel and Doumer<sup>21</sup> observed a case with the clinical syndrome of paroxysmal hypertension. The first tumor of this nature to be removed at operation was the case of Masson and Martin.<sup>22</sup> The patient died of shock, which the authors considered incommensurate with the severity of the operation. Recently, Riemer<sup>23</sup> reported a cystic tumor of this type in association with Addison's disease. Furthermore, malignant tumors, as evidenced by the formation of metastases, were described by Bonnamour,

\* 14. Laignel-Lavastine and Aubertin: Adénome médullaire de la capsule surrénale (médullome surrénale) chez un tuberculeux mélanodermique, Arch. de méd. expér. et d'anat. path. **20**:818, 1908.

15. Neusser, E., and Wiesel, J.: Die Erkrankungen der Nebennieren, ed. 2, Vienna, Alfred Hölder, 1910, p. 97.

16. Herde, M.: Zur behre der Paragangliome der Nebenniere, Arch. f. klin. Chir. **97**:937, 1912.

17. Albrecht: Ueber Hamartome, Verhandl. d. deutsch. path. Gesellsch. **7**:153, 1904.

18. Helly, C.: Zur Pathologie der Nebenniere, München. med. Wchnschr. **33**: 1811, 1913.

19. Hedinger, E.: Struma medullaris cystica suprarenalis, Frankfurt. Ztschr. f. Path. **7**:112, 1914. 1911

20. Harbitz, F.: Tumors of the Sympathetic Nervous System and the Medulla of the Suprarenal Glands, Especially Malignant Neuroblastomas, Arch. Int. Med. **16**:324 (Aug.) 1915.

21. L'abbé, Tinel and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982, 1922.

22. Masson, P., and Martin, J. F.: Paragangliome surrénale, étude d'un cas humain de tumeurs malignes de la medullo-surrénale, Bull. de l'Assoc. franç. p. l'étude du cancer **12**:135, 1923.

23. Riemer, R.: Sobre un caso de syndrome de Addison produzio por "Paraganglioma da capsula supra-renal," Folha med. **8**:33, 1927.



Doubrow and Montequé<sup>24</sup> and Masson.<sup>25</sup> The former quoted a description of another malignant case, from Gravier and Bernheim. Other tumors of this kind illustrating the characteristics of structure and a variety of associated clinical conditions were described by the following authors: Kawashima,<sup>26</sup> Wegelin,<sup>27</sup> Herxheimer,<sup>28</sup> Orth,<sup>29</sup> Thomas,<sup>30</sup> Bergstrand,<sup>31</sup> Biebl and Wichels,<sup>32</sup> Zwecker,<sup>33</sup> Oberling and Jung<sup>34</sup> and Schroeder.<sup>35</sup>

*Pheochromocytoma of Other Chromaffin Organs.*—These tumors are not confined to the suprarenal medulla. They may occur wherever chromaffin tissue is found. The first tumors of this nature to be noted in the carotid gland were described by Marchand<sup>36</sup> and by Paltauf.<sup>37</sup> Since that time, about eighty tumors in this location have been reported. The organ of Zuckerkandl was involved in a number of reported cases; the first was reported by Stangl,<sup>38</sup> and the latest by Handschin.<sup>39</sup> To this

24. Bonnamour, Doubrow and Montequé: Sur le comportement des métastases pleurales des paragangliomes, *Ann. d'anat. path.* **4**:141, 1927.

25. Masson, P.: Tumeurs: Traité de pathologie médicale et de thérapeutique appliqué XXVII; Diagnostics de Laboratoire II, Paris, A. Maloine et fils, 1923, p. 596.

26. Kawashima, K.: Ueber einen Fall von multiplen Hautfibromen mit Nebennierengeschwulst, *Virchows Arch. f. path. Anat.* **203**:66, 1911.

27. Wegelin, C.: Ueber einen chromaffinen Tumor der Nebenniere, *Verhandl. d. deutsch. path. Gesellsch.* **15**:255, 1912.

28. Herxheimer, G.: Ueber Tumoren des Nebennierenmarks, *Beitr. z. path. Anat. u. z. allg. Path.* **57**:112, 1914.

29. Orth, J. J.: Ueber eine Geschwulst des Nebennierenmarks nebst Bemerkungen ueber die Nomenklatur der Geschwülste, *Sitzungsber. d. deutsch. Akad. d. Wissensch.*, Berlin, G. Reimer, 1914, no. 1.

30. Thomas, E.: Ein chromaffine Tumor der Nebenniere: Ein weitere Beitrag zu den Markgeschwülsten der Nebenniere, *Frankfurt. Ztschr. f. Path.* **16**:376, 1915.

31. Bergstrand, H.: A Case of Pheochromocytoma of the Suprarenal Gland with Hypertrophy of the Myocardium of the Left Ventricle, *Hygieia* **83**:321, 1920.

32. Biebl, M., and Wichels, P.: Physiologische pathologisch-anatomische Betrachtungen in Anschluss an einen Fall von Pargangliom beider Nebennieren, *Virchows Arch. f. path. Anat.* **257**:182, 1925.

33. Zwecker, I. T.: Chromaffine Tumor of the Adrenal Medulla, *Boston M. & S. J.* **192**:254, 1925. *wrong reference vol. 193. Zeckwer.*

34. Oberling, C., and Jung: Paraganglioma de la surrenali avec hypertension, *Bull. et mém. Soc. méd. d. hôp de Paris* **10**:366, 1927.

35. Schroeder: Doppelseitiges Nebennierenparagangliom, *Centralbl. f. allg. Path. u. path. Anat.* **41**:483, 1927-1928.

36. Marchand, F.: Beiträge zur Kenntnis der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren, *Beitr. z. Wissensch. Med. Festschr. f. Virchow*, 1891, vol. 1, p. 535.

37. Paltauf, R.: Ueber Geschwülste der Glandula carotica, *Beitr. z. path. Anat. u. z. allg. Path.* **11**:260, 1892.

38. Stangl, E.: Zur Pathologie der Nebenorgane des Sympathicus, *Verhandl. d. deutsch. path. Gesellsch.* **5**:250, 1902.

39. Handschin, E.: Zur Kenntnis den Zuckerkandlschen Organe, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:728, 1928.

group possibly belongs the case associated with paroxysmal hypertension in which operation was performed by Mayo.<sup>40</sup> Alezais and Peyron<sup>41</sup> described a chromaffin cell tumor in the sacrococcygeal region and gave the name paraganglioma to the entire group, considering it a neoplasm of the paraganglion, as described by Kohn.<sup>1</sup>

Pheochromocytomas of the suprarenal medulla in animals were described by Stilling<sup>42</sup> and by Zangfrognini.<sup>43</sup>

#### REPORT OF A CASE

*History.*—A Polish woman, aged 45, when admitted to the Mount Sinai Hospital, on June 3, 1927, complained of a cough that had troubled her for four months. For ten years, she had had palpitation and dyspnea on slight exertion and a tremor of the hands. She had been considered as having exophthalmic goiter and had been treated by means of roentgen rays for a suspected substernal goiter. She had been unsuccessfully operated on a number of times for sterility. For the past few years, she had been vomiting about once a week. This had become more frequent, so that, for from four to five months before admission, she had been vomiting almost nightly.

*Examination.*—A physical examination disclosed a moderate degree of exophthalmos, a marked tremor and hypertrichosis of the chin. Her blood pressure on several examinations varied from 226 systolic and 108 diastolic to 177 systolic and 122 diastolic. During her stay in the hospital, her temperature ranged from 103 to 104 F. A week after her admission, she began to exhibit twitchings of the hands and face, and she lapsed into a semistuporous state. Her neck was stiff and Kernig's sign was positive. The pupils were markedly contracted. The nitrogen content of the blood was normal. The meningeal signs became more marked, and she died in coma.

The clinical diagnosis was Grave's disease and chronic nephritis with hypertension.

*Autopsy* (by Dr. Paul Klemperer).—The body was well developed. There was hypertrichosis of the chin. The eyes were slightly bulging.

*Chest:* The lower lobe of the right lung was completely shrunken. It was composed of dense, white connective tissue, in which were seen a few areas of lung tissue. The pleura was densely adherent. The bronchus of the right lower lobe was extremely stenosed. There were several hemorrhagic infarcts in the left lower lobe. The branch of the pulmonary artery leading to this lobe contained a riding embolus, the ends of which showed fresh thrombi extending distally.

*Heart:* The pericardial sac was covered with a bilobed, fleshy thymus. The heart weighed 515 Gm. There were numerous ecchymoses in the epicardium. All the chambers were hypertrophied and somewhat dilated. There was a slight

40. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, *J. A. M. A.* **89**:1047 (Sept. 24) 1927.

41. Alezais and Peyron: Un groupe nouveau de tumeurs epitheliales: Les paragangliomes, *Compt. rend. Soc. de biol.* **38**:745, 1908.

42. Stilling, M. H.: A propos de quelques expériences nouvelles sur la maladie d'Addison, *Rev. de méd., Paris* **10**:808, 1890.

43. Zangfrognini, A.: Adenoma di tessuto cromaffine della capsula surrenale, *Sperimentale, Arch. di biol.* **58**:812, 1903.

thickening at the line of closure of the mitral valve, but not any evidence of old or recent endocarditis. There was a slight sclerosis of the right coronary artery. The left coronary artery was wide. The pulmonary artery showed lipoid patches. The aorta had lost its elasticity. Its intima showed yellow sclerotic patches throughout its extent. The peripheral vessels showed a slight intimal thickening.

**Spleen, Liver and Suprarenal Glands:** The spleen weighed 110 Gm., and showed evidence of chronic passive congestion. The liver weighed 1,025 Gm. It was firm and brown, with a distinct lobular structure. The right suprarenal gland was the seat of a tumor, which will be described later in detail. The left suprarenal gland was normal in shape and position. Its cortex measured 1.2 mm. in width. The medulla was from 3 to 4 mm. wide.

**Kidneys:** The right kidney weighed 170 Gm. It showed a distinct flattening of its upper pole. The capsule stripped with ease, revealing a smooth brown surface, which showed numerous small ecchymoses. On section, it did not show any abnormality. The left kidney weighed 135 Gm. On section, it showed a few sharply defined hemorrhagic areas within the cortex. There was a red thrombus in the renal vein.

**Gastro-intestinal Tract, Thyroid Gland, Pancreas, Ovaries and Uterus:** The gastro-intestinal tract disclosed a few small polyps of the large intestine. The thyroid was small and granular. The pancreas appeared normal. The right ovary was wrinkled, small and fibrous. The left ovary was missing. The uterus was small and atrophic. Its endometrium was atrophic.

*Microscopic Examination.*—**Thyroid:** The acini of the thyroid gland were filled with pink and bluish colloid. The septums were fibrous. The epithelium was low. Evidence of hyperplasia or lymphocytic infiltration was absent.

**Lungs:** The lungs were congested. There was an area of hemorrhagic infarction with a thrombus at its apex. The arterial walls were thickened. The right lower lobe showed the acini replaced by dense acellular connective tissue with thickened, almost completely obliterated arteries, partly recanalized. There were occasional medial calcifications. Within this fibrous tissue there were many glandlike structures with low cuboidal epithelium.

**Aorta, Heart and Pulmonary Artery:** There was intimal proliferation of the aorta with lipoid changes. The media showed calcification and small round cell foci. The adventitia showed arteriosclerosis of the nutrient vessels and narrowing of their lumen. The heart showed hypertrophy of the muscle fibers. There was a slight arteriosclerosis of the branches of the coronary arteries. The pulmonary artery showed a moderate degree of intimal proliferation.

**Liver:** The liver showed central hyperemia with necrosis of the hepatic cells. There was a conspicuous arteriosclerosis of the branches of the hepatic artery. Some of the smaller arterioles were hyalinized.

**Pancreas and Spleen:** In the pancreas, thickening and hyalinization of the small arterioles were noticeable. The spleen showed marked arteriosclerosis and congestion.

**Kidneys:** The kidneys revealed moderate arteriosclerosis of the arcuate and interlobular arteries, and conspicuous hyalinization of the arterioles. Most of the glomeruli did not show any changes, but a number of them contained hyaline material within the tufts. A few of these glomeruli showed markedly engorged capillaries. There was intense congestion in the region about these glomeruli. The tubular epithelium, in general, was not altered except in the regions of the infarcted glomeruli, where epithelial necrosis was encountered.

**Suprarenal Gland and Brain:** The left suprarenal gland showed the medulla abundant. Within the medulla were a considerable number of round cell foci. The cortex was wide and rich in lipoids. The brain did not show any changes. The meninges did not show any evidence of inflammation.

#### THE TUMOR

The right suprarenal gland was unusually large and round. It lay on the upper pole of the right kidney, which was flattened. On section, almost the entire structure was seen to be replaced by a round encapsulated tumor, 4 cm. in diameter. At the upper pole there was a cap of suprarenal cortex and medulla, normal in appearance. Surrounding the tumor was a fibrous capsule, which blended with the yellow cortex. At the medial surface was a projecting portion

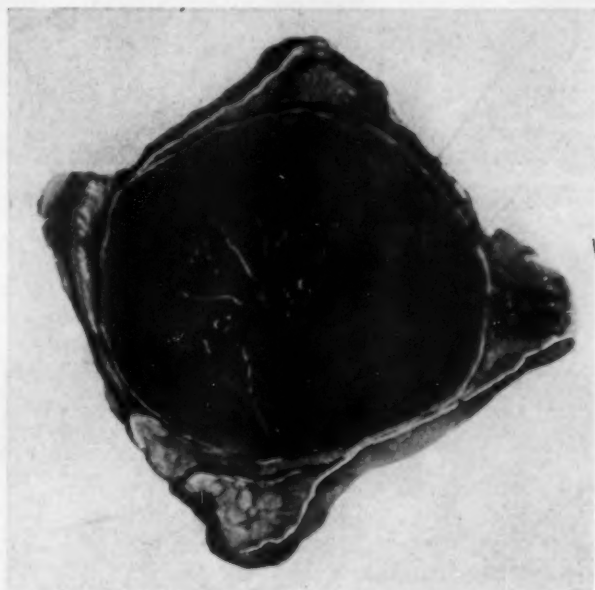


Fig. 1.—A section of the right suprarenal gland showing the encapsulated tumor with a well preserved cortex. Above the tumor is a cap of normal suprarenal gland with normal medulla. To one side there is normal medulla separated from the tumor by the capsule. (Natural size.)

of cortex and wide medulla, which was demarcated from the encapsulated tumor. The tumor tissue was rather soft, homogeneous and reddish brown; it showed areas of hemorrhage.

**Microscopic Examination.**—The capsule, which was rather thick, consisted of connective tissue and flattened cortical cells. The cortex in most places was flattened. Separated from the tumor by the capsule were two areas of medullary tissue, which presented a normal appearance. The tumor consisted of anastomosing cords and islands of large polyhedral cells irregular in shape and varying from 15 to 45 microns in diameter. The cytoplasm, which was abundant, appeared finely granular and stained bluish red with hematoxylin-eosin. In formaldehyde-fixed specimens, the cells varied in their affinity for hematoxylin.



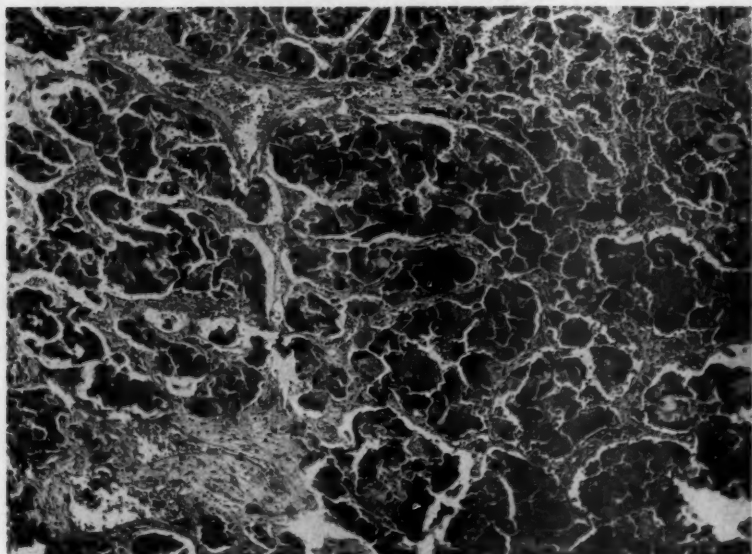


Fig. 2.—Islands of cells separated by vascular stroma. The scattered darker cells show the chromic reaction. (Magnification,  $1 \times 200$ .)

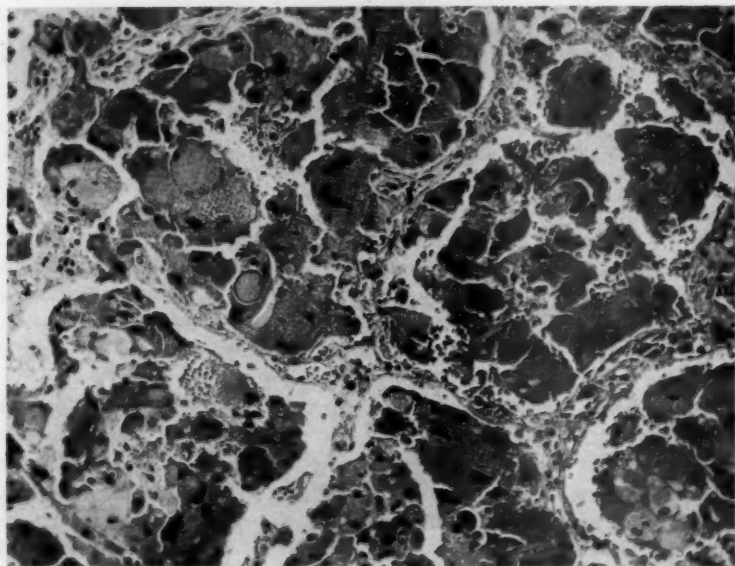


Fig. 3.—Higher magnification of the same field as shown in figure 2, showing the lack of stroma between the cells of the alveolae, their syncytial arrangement, their varying size, the shape and the staining qualities of the nuclei and the colloid inclusions. (Magnification,  $1 \times 400$ .)



Scattered cells were markedly basophil and stained deeply with hematoxylin. The same variance was shown in the specimens fixed in formaldehyde-Müller. After fixation with chromic salts, the cytoplasm of some of the cells stained yellowish brown. This yellow-brown color was independent of the granulation of the cytoplasm. It was present between the granules. In specimens stained with carmine, the yellow-brown color showed up especially well and appeared to be present in the nuclei and in the nucleoli. The nuclei were large; some were round, some oval and some rather irregular. They varied in their staining capacity; most contained a dense chromatin network and were pyknotic, some were vesicular. In general, the nuclei took a deeper stain than those in the normal medulla. They contained one or more distinct, large, round nucleoli. Within the cytoplasm, and also between the cells, there were occasional large and small spherical and ovoid bodies, which stained deeply with eosin and had a hyaline appearance. They did not react with chromic salts. They stained blue with Mallory's aniline blue and were not affected by Mallory's phosphotungstic acid hematoxylin. Rarely, there were found scattered among the typical cells of the tumor, single large, bizarre cells, each measuring about 70 microns and containing a large, irregular, deeply staining nucleus and a clear cytoplasm, which did not show the chromic reaction.

In places, there was an infiltration of the stroma by leukocytes and plasma cells; occasionally, by small cells, larger than lymphocytes, with scanty cytoplasm, the nuclei of which showed a dense chromatin network. These might possibly be considered as sympathogonia. The cords and islands of cells were separated by numerous capillaries and fine strands of connective tissue, which in places also showed the chromic reaction. There were many small hemorrhagic areas, and areas of vacuolar degeneration and necrosis of the tumor tissue. Sudan stain showed the absence of fat. Iron pigment was absent. One of the larger veins contained a fresh thrombus. A number of the veins contained tumor cells.

*Chemical Examination.*—A portion of the tumor was macerated in saline solution and the extract examined for the presence of epinephrine qualitatively by the method of Ewins.<sup>44</sup> It showed a strongly positive reaction. Examined quantitatively by the method of Folin, Cannon and Dennis,<sup>45</sup> the tumor, which weighed 40 Gm., was found to contain 1.5 mg. of epinephrine per gram of tumor tissue. The total epinephrine content of the tumor, as shown by this method, would therefore be 60 Gm. The organ was removed seven and a half hours after death, and the test was carried out on the following day. Since epinephrine is rapidly destroyed in the tissues after death, the epinephrine content during life might have been considerably greater.

#### SUMMARY OF THE CASE

The case, then, was that of a woman, aged 45, who for many years had been suffering from hypertension together with nervous manifestations similar to those of exophthalmic goiter. She had fever for about one week, developed signs of meningitis and died in coma. At autopsy, there were found a marked hypertrophy of the heart, generalized arterio-

44. Ewins, A. J.: Some Color Reactions of Adrenine and Allied Bases, *J. Physiol.* **40**:317, 1910.

45. Folin, O.; Cannon, W. B., and Dennis, W.: A New Colorimetric Method for the Determination of Epinephrine, *J. Biol. Chem.* **13**:477, 1912-1913.

sclerosis and arteriosclerosis, chronic passive congestion of the viscera, infarcts of the lungs and a pheochromocytoma of the medulla of the right suprarenal gland. The suprarenal tumor showed areas of necrosis and hemorrhage with venous thrombi.

Although there were pathologic evidences of cardiac insufficiency, the clinical picture was not that of death due to cardiac failure. In the absence of lesions of the brain or the meninges to account for the meningeal symptoms, and in the absence of a focus of inflammation to explain the fever, the similarity of the clinical condition to cases of suprarenal hemorrhage as described in the literature suggests the possibility that necrosis and hemorrhage within the tumor caused death in this case.

#### REVIEW OF OTHER REPORTED CASES

Thirty other cases of tumors of this type are reported in the literature. The reports reveal facts of such clinical and pathologic interest that it is thought wise to make them more available by means of the following summary:

*Occurrence with Regard to Sex and Age.*—The tumor occurred more often in women than in men; namely, in eighteen women and in six men. The incidence was greatest in older people. The first five cases reported were in persons over 60 years of age. Subsequent reports showed its predominance in the fourth, fifth and sixth decades. Neusser and Wiesel<sup>16</sup> described a case in a 2 year old infant.

*Location.*—Thirteen were in the right suprarenal gland, nine were in the left and six were bilateral. Kolisko's case (cited by Neusser and Wiesel<sup>16</sup>) showed, in addition, a third tumor, separated from the suprarenal gland, a chromaffin cell tumor over the right kidney, evidently a tumor of a medullary rest. Harbitz<sup>20</sup> reported a tumor of the left suprarenal gland associated with an additional tumor of a similar nature over the left kidney.

*Gross Appearance.*—The largest tumors were those reported by Suzucki<sup>18</sup> and Hedinger.<sup>19</sup> They measured 10 cm. in diameter; both were cystic. The smallest tumors reported were the size of a pea. The smaller tumors were grayish in appearance; the larger ones were red and hemorrhagic, and sometimes dark brown, as a result of old hemorrhages. They were located distinctly within the medulla and were well encapsulated, the cortex being thinned out over them.

The cases of Berdez, Suzucki, Laignel-Lavastine and Aubertin, Wegelin, Herde (case 2), Thomas, Biebl and Wichels, as well as the case I have reported showed the presence of a normal medulla separated from the tumor by a capsule. The tumors often showed hemorrhages and were prone to undergo partial necrosis and to become cystic (Suzucki, Kolisko, Herde [2 cases], Hedinger, Thomas, Riemer). Often the cysts were multiple.

*Microscopic Appearance.*—The microscopic picture in other reported pheochromocytomas agrees, in general, with that in my case. The tumors consisted either of nests or of cords of polyhedral cells separated by thin connective tissue stroma, rich in capillaries, giving the tumors either an alveolar or a trabecular appearance. Nine cases were described as trabecular, six cases as having a definite alveolar formation and three cases as showing both types of arrangement in different portions of the tumor. The predominating element of these tumors was always described as a polyhedral cell, somewhat larger than the cell of the

normal suprarenal medulla, and having an abundant, finely granular cytoplasm, varying greatly in size, and a rather large nucleus containing a chromatin network which stained more deeply than that of the normal vesicular nucleus seen in the normal medulla. Mitoses were rare. Most of the cases contained many multinucleated cells. The nuclei showed one or more large nucleoli. Single large bizarre cells with giant pyknotic nuclei were observed in many of the cases. Hedinger considered the possibility of their being ganglion cells. They did not, however, show any of the characteristics of ganglion cells except for their size. In all cases, the affinity of the cells for chromic salts was variable. The chromaffin cells were scattered between similar cells which took the chromic stain little or not at all.

The presence of hyaline inclusions within the cells of the tumor was first noted by Manasse, and since then the hyaline inclusions have been seen in most of the cases. They have the appearance of the inclusions seen in the cells of the normal suprarenal medulla, but are much larger.

Manasse, Wegelin and Thomas described a diffuse brown staining of the interstitial tissue by the chromic salts. Suzucki and Herde noted that the cytoplasm of the pheochromocytes was stained brown diffusely between the cytoplasmic granules.

Ganglion cells, together with unmedullated nerve fibers, were noted by Marchetti and Hedinger. Cells with pyknotic nuclei, having the appearance of sympathogonia, were described in half the reports of cases. The difficulty of differentiating these from ordinary lymphocytes makes it hazardous to force an explanation of their presence.

Manasse and Biebl and Wichels found many of the specific cells within the larger veins. Suzucki observed a chromaffin cell in an artery and brown masses within the veins.

*Epinephrine Content.*—Qualitative tests for epinephrine were performed chemically or biologically on extracts of the tumor tissue in a number of the reported cases. In all cases so examined, the presence of epinephrine was demonstrated. Quantitative determinations were not made.

*Glycogen.*—The presence of glycogen was variable. Thus, Herde was able to demonstrate the presence of glycogen in his first case but not in his second. Hedinger reported a similar experience.<sup>46</sup>

*Associated Conditions.*—Certain clinical observations in the reported cases deserve mention. Thus: neurofibromatosis as a concomitant condition was observed in four cases (Suzucki, Kawashima, Herxheimer, Zwecker). Hypertension independent of renal disease was present clinically in nine of the latest twenty cases (those reported by Neusser and Wiesel, Helly, Orth, Bergstrand, L'abbé, Tinel and Doumer, Biebl and Wichels, Oberling and Jung, Schroeder, and the one reported here). Neusser and Wiesel's case was in a child, aged 2 years. In two additional cases, in which a clinical report was not recorded, there were pathologic evidences of hypertension. Thus, in the case of Thomas, there was hypertrophy of the left ventricle, and in Herde's case 2 there were hypertension and cardiac hypertrophy, with a primary, genuine contracted kidney. Recently, paroxysmal hypertension was observed by Oberling and Jung and by L'abbé, Tinel and Doumer. The patients in these cases were only 28 years of age. Four cases of glycosuria have been described (Herde's case 1, the cases of Helly, Biebl and Wichels, L'abbé, Tinel and Doumer). In the first two,

46. Hedinger, E., in discussion of Wegelin (footnote 27).

mention is not made of the condition of the pancreas, and in the other two the pancreas is described as having been normal grossly and microscopically."

A number of the cases presented symptoms of vasomotor or sympathetic instability, or shock. Thus, Kolisko's patient died two hours after the administration of a 2.5 per cent solution of cocaine preceding the extraction of a tooth. Herde's patient died shortly after the simple amputation of a gangrenous extremity. Masson's patient died, after the removal of the tumor, in deep shock, which, in the opinion of the author, was incommensurate with the operative trauma. Oberling and Jung's patient went into shock and died immediately after a normal delivery. Helly's patient died after an operation for fistula in the anus and for hemorrhoids, under local anesthesia. A case that deserves special mention was that of a patient of L'abbé, Tinel and Doumer: A woman, aged 28, exhibited attacks of paroxysmal hypertension, each ushered in by an intense emotional reaction. The attacks were accompanied by marked pallor and tremor and were followed by nausea, a sense of constriction in the abdomen and vomiting, with urinary suppression. Pressure on the eyeballs caused a drop in the blood pressure from 280 to 104 and was followed by generalized vasodilation and glycosuria. The patient suffered two attacks of pulmonary edema.

Another pathologic condition of interest associated with pheochromocytoma was the colloid adenoma of the thyroid found together with a large adenoma of the liver by Hedinger. Still another was that found by Harbitz, in examining a tumor of the left suprarenal gland; namely, a cystadenoma of the pancreas and a hypernephroma of the left kidney with a pheochromocytoma between that kidney and the tumor-containing suprarenal gland—a combination in one case of hyperplasias of misplaced rests of both the suprarenal cortex and the medulla.

Arteriosclerosis was found regularly in the cases associated with hypertension. Neusser and Wiesel considered the arterial lesions in their case (medial necrosis) as typical of suprarenal sclerosis. Biebl and Wichels discussed the significance of arteriosclerosis in these cases at length. They believed that a direct relationship between the tumor and the clinical manifestations is evident. They explained the absence of medial necrosis in the lesions produced experimentally with epinephrine as due to the differences between the human and the animal subject. While this explanation may be valid with respect to the absence of medial necrosis, it does not afford evidence that the arteriosclerotic lesions are caused by a hyperadrenalinemia. In the absence of the specific medial lesions, one must consider the arteriosclerosis as more probably due to the mechanical effect of the hypertension.

#### COMMENT

From the foregoing facts, one may draw certain conclusions concerning this type of tumor. It is, without doubt, a neoplastic growth of a portion of the suprarenal medulla. The perfect encapsulation and the presence of a normal medulla outside of the tumor show that it is not a diffuse medullary hyperplasia.

Usually, the tumor is benign. It is perfectly encapsulated, does not give rise to metastases and does not cause a cachectic state. Those who feel that it is malignant mention the irregular size and character of the cells, and the tendency to hemorrhage and degeneration. These proper-

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47. Recently, Schroeder reported a case with glycosuria and atrophy of the pancreas.



ties may be more properly evaluated, however, when one considers the structure of the tissue from which the tumor arises, which also possesses similar characteristics. Nevertheless, as has been mentioned, malignant tumors of a similar nature have been reported. The available information concerning them is meager, especially in respect to the epinephrine content of the tumors and their metastases.

Various authors have considered the tumor as a hamartoma (Herxheimer, Herde, Dietrich<sup>48</sup>). There is considerable evidence against this view. The tumor evidently arises from a mature cell—the pheochromocyte—and occurs in persons of middle age and old age, when the process of differentiation of pheochromocytes from sympathogonia has been completed. The malignant embryonal tumors occur before puberty, the time when maturation is complete (Wiesel). Encapsulation is not a characteristic of the hamartomas, which are embryonal malformations and do not belong to the group of new growths (Albrecht). In regard to similar tumors in misplaced suprarenal rests (Harbitz, Weichselbaum and Greenisch<sup>49</sup>), one may rightly consider the conception of hamartoma, but not in the case of a tumor arising from mature elements in their normal location.

Degeneration, necrosis and cyst formation are characteristic of these tumors. The cyst fluid has never been tested for the presence of epinephrine. It seems probable that among the growths reported as cysts of the suprarenal gland there are a number that are really cystically degenerated pheochromocytomas.

It is evident that the tumor is actively secretory. Microscopically, the chromaffin reaction, as shown by Ogata,<sup>50</sup> is direct evidence of the presence of a strong reducing substance, which is, in all probability, epinephrine. This substance exists in a fluid state. It is independent of the cytoplasmic granules of the pheochromocytes. It permeates the cells and the surrounding tissues.

The cellular structure is similar to that of the normal suprarenal medulla. The hyaline inclusions seen in the normal suprarenal medulla have been repeatedly found in the tumor. I have shown that in their staining reactions with phosphotungstic acid hematoxylin and Mallory's aniline blue they do not show any resemblance to similar droplets that are the products of degeneration, nor in fact to other hyaline types of

48. Dietrich, A., and Siegmund, H.: Die Nebenniere und das chromaffine System, in Lubarsch and Henke: Handbuch der speziellen pathologischen Anatomie, Berlin, 1926, vol. 8, p. 1049.

49. Weichselbaum and Greenisch: Das Abenome der Niere, Wien. med. Jahrb., 1883, p. 221.

50. Ogata, T., and Ogata, A.: Ueber die Henlesche Chromeatation der sogenannten chromaffinen Zellen und den mikrochemischen Nachweis des Adrenalins, Beitr. z. path. Anat. u. z. allg. Path. 71:376, 1923.



degeneration. Furthermore, I have been able to confirm Biebl and Wichels' observation that they are best seen in the better preserved portions of the tumor. These observations speak strongly against the theory that the droplets are degenerative in nature. The additional fact that they are found within cells of a secretory type indicates that they are products of secretion. That they do not show the histochemical reactions of epinephrine leads one to the hypothesis that they represent an intermediary phase of the secretion of epinephrine.

The epinephrine content, as shown by chemical and biologic tests, gives further proof that the tumor secretes. The amount of epinephrine in this case, as shown by quantitative examination, was far greater than that reported in normal suprarenal glands.

Outstanding in this review is the large percentage of cases associated with hypertension and signs of vasomotor or autonomic instability. The occurrence of hypertension at an early age, the inability of so many of these patients to withstand minor operative procedures and the sudden death without demonstrable cause in this case appear also to be more than simple coincidences. Furthermore, the occurrence of glycosuria demands explanation. It is well known that epinephrine can cause such clinical manifestations, and it is tempting to assume that these manifestations are due to the action of the epinephrine that has been shown to be secreted by the tumor. That it really is the cause of the clinical symptoms in the cases here reviewed, however, can be proved only by the demonstration of an increased absorption of epinephrine from the tumor. The only evidence available in this connection is the vascularity of the tumor, which suggests the possibility of absorption.

Manasse<sup>51</sup> and Biebl and Wichels, who observed cellular constituents of the tumor within the veins, considered that a pressor substance might be transmitted in this way. In fact, the former considered this the mechanism for the distribution of epinephrine from the normal suprarenal gland. However, one should not lay too much emphasis on the importance of this observation. Liver cells singly and in groups are seen repeatedly within the portal veins in microscopic sections. I have even seen an entire glomerulus in one of the branches of the renal vein, and Suzucki reported the finding of a chromaffin cell in an artery in his case. Such observations lead one to conclude that this is probably the result of a technical artefact and to minimize the validity of the conclusions drawn from it. Anatomic proof of the absorption of epinephrine is lacking.

Chemical proof of the causal relationship between the clinical states and the tumor would consist in the demonstration of hyperadrenalinemia.

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51. Manasse, P.: Ueber die Beziehungen der Nebennieren zu den Venen und dem venösen Kreislauf, *Virchows Arch. f. path. Anat.* **135**:263, 1894.

However, such a demonstration is impossible with the present methods. A similar difficulty lies in the way of proving that increased absorption of epinephrine is the cause of hypertension. The presence of increased amounts of epinephrine in the suprarenal glands in hypertension has been reported by a number of workers.<sup>52</sup> However, in addition to other conflicting facts that discredit the theory, is the fact that increased absorption of epinephrine has not been demonstrated.

It is perhaps advisable to offer some justification for the term pheochromocytoma. The tumor has been known variously by the names angiosarcoma, perithelioma, struma medullaris cystica suprarenalis, paraganglioma and chromaffin cell tumor. The first three names may be excluded for obvious reasons. The term paraganglioma was originated by Alezais and Peyron in 1907 in describing a tumor of the sacrococcygeal region. It was derived from the name paraganglion, which was applied by Kohn to the chromaffin system, appropriate since it described the embryonic origin of the system. Pick,<sup>53</sup> however, suggested the advisability of naming the tumor from the predominating type of cell—in this case the pheochromocyte, the name of which, originated by Poll, is generally accepted. It appears especially advisable to use the name of the mature chromaffin cell, because of the parallelism between this tumor and the ganglioneuroma, which was named after the mature sympathetic cell, which is developed from the same anlage.

#### SUMMARY AND CONCLUSIONS

A case of pheochromocytoma of the suprarenal medulla associated with hypertension is reported. This tumor is benign. It arises from the mature pheochromocyte. It is not a hamartoma.

The hyaline droplets found in the cells of the tumor as well as of the normal suprarenal medulla are differentiated from the hyaline droplets of degeneration by the staining reactions. The droplets probably represent an intermediary state of the secretion of epinephrine. The tumor is actively secretory. Quantitative examination shows that it contains a total amount of epinephrine much in excess of that which is found in normal suprarenal glands at autopsy.

A large percentage of the cases reported in the literature presented clinical symptoms that might well be explained as due to the absorption of excessive amounts of epinephrine. That these clinical conditions are really caused by the action of epinephrine absorbed from the tumor can be proved only by the demonstration of an increased concentration of epinephrine in the blood.

52. Dietrich, H., and Siegmund, H. (footnote 48, p. 994).

53. Pick, L.: Das Ganglioma embryonale sympathicum, *Berl. klin. Wchnschr.* 49:16, 1912.

# THE EFFECT OF ELECTRIC CURRENTS ON THE ARTERIES

A HISTOLOGIC STUDY \*

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It is still a matter of discussion whether electric currents in passing through the body produce typical anatomic changes or whether these changes are merely the result of the heat into which the electric energy is transformed in a conductor of the resistance of the living tissues. This question has been taken up especially with regard to the so-called current markings of the skin, and most investigators, including those who emphasize their diagnostic value, consider them an effect of the high temperature at the point of entrance and exit of the current, which causes a coagulation and boiling of the tissues.

The arterial lesions found in the vicinity of electric burns are of great practical importance, since they may lead to severe hemorrhages, hours or even days after the accident, and since they often make ligation of the injured blood vessel impossible. Jellinek<sup>1</sup> called attention to the great fragility of the arteries in and around electric wounds. Balkhausen and Gruter described an extensive destruction of the nuclei of the media of the arteries. Martin Couvert and Dechaume observed a disintegration of the muscular elements of the media of the arteries associated with a separation of the internal elastic membrane from the media. Dickens found severe inflammatory changes in the arteries of both forearms following an injury by lightning stroke. Bolongnesi reported microscopic observations of the blood vessels of rabbits through the hind limbs of which a domestic current had been sent. There were multiple ruptures of the elastic fibers with thrombosis and hemorrhages.

The importance of the subject and the scarcity of the available data induced us to perform a series of experiments in which arteries of dogs were exposed to electric currents. Low tension currents only were used because they produce changes which lend themselves better to a microscopic analysis than the severe destructions that result from currents of high voltages.

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\* From the Department of Pathology, University of Illinois.

1. For the literature, reference should be made to the senior writer's review on electropathology, Arch. Path. 5:837, 1928.

Since in experiments of this nature the technic is of great importance, it will be described in some detail.

#### METHODS

The experiments were performed under sterile conditions on adult dogs. Under ether anesthesia, the femoral artery below Poupart's ligament was dissected out for a distance of 5 cm. A small branch, found usually near the lower end, was ligated and cut. A thin rubber sheet was spread underneath the artery in order to isolate it as much as possible. Twisted strips of gauze soaked with a physiologic saline solution served as electrodes. They were wound around the vessel twice without constricting it, and were placed at a distance of 2.5 cm. in such a manner that at each end there remained a free arterial segment at least 1 cm. in length. This precaution was necessary in order to avoid too great a

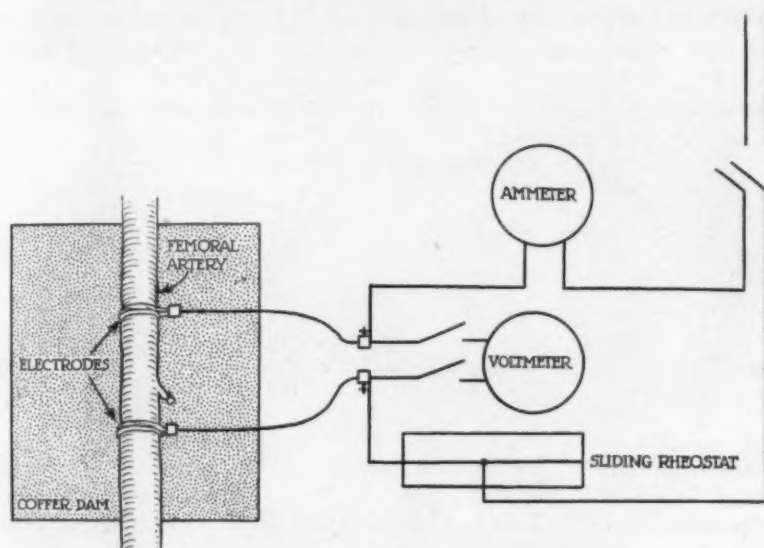


Fig. 1.—The set-up used in the experiments for the passage of the electric current through the femoral artery of a dog.

loss of the current from passage around the electrodes through the body of the animal. The electrodes were connected with copper wires. The current was controlled by a sliding resistance of 3,000 ohms, and the intensity and tension were measured by an ammeter registering from 25 to 125 milliamperes and a voltmeter with a range of from 25 to 150 volts (see fig. 1). Alternating currents of 110 and 220 and a direct current of 110 volts were used. The alternating and the direct current had the same effect. The currents were sent through the vessel for two minutes, four shocks, each of thirty seconds duration, usually being given. As soon as the current was closed, the muscles of the extremity were thrown into tetanic contractions, and, also, the portion of the vessel between the electrodes was contracted, the latter contraction persisting for from one to two minutes after the current had been broken. There was, however, a great variation in the intensity of the arterial contraction. In some of the experiments it was hardly visible; in others the vessel became almost colorless. An interesting



observation was the great fluctuation of the resistance of the vessel during the experiment, which often made the reading of the ammeter difficult. For reasons to be discussed later, it was deemed necessary to study the effect of the electric current when the circulation was interrupted. In these experiments, the artery was clamped at a point distal to the electrodes with a small clamp the branches of which were covered with rubber.

In order to determine whether anatomic changes might result from the mere handling of the vessel, we duplicated the experiments without applying the current.

After the experiment, the wound was closed by a double silk suture and covered with iodine collodium. The dogs were killed about a week later, and the vessels were fixed immediately with a 10 per cent solution of formaldehyde. A summary of the experiments is given in the table.

## COMMENT

While in the first experiment the passage of the current through the artery had led to severe changes, lesions were not encountered in the

*A Summary of the Experiments That Were Made to Determine the Cause of the Severe Arterial Changes Seen in Burns Due to the Passage of an Electric Current*

No.	Current Used,* Volts	Circulation	Amperage (MA)	Voltage	Duration, Minutes	Result
1.....	110 A. C.	?	30	—	2	Severe changes
2.....	110 A. C.	Free	30	—	2	No changes
3.....	110 A. C.	Free	35-50	—	2	No changes
4.....	110 A. C.	Free	50	20	2	No changes
5.....	110 A. C.	Free	50	65	2½	No changes
6.....	220 A. C.	Free	75	150	1½	No changes
7.....	110 A. C.	Stopped	55	80	1½	Severe changes
8.....	110 D. C.	Stopped	60	100	2	Severe changes
9.....	110 D. C.	Free	55	100	2	No changes
10.....	108 D. C.	Stopped	65	95	1½	Severe changes
11.....	108 D. C.	Free	65	90	2	No changes

\* A. C. means alternating current; D. C., direct current.

five experiments that followed, although they were conducted under apparently the same conditions. In an attempt to explain this striking difference of the results, it seemed most likely that in the first experiment the electrodes had been wound around the artery so tightly that the lumen had been unintentionally obstructed. With this point in view, the experiments were repeated and the circulation was interrupted at a point distal to the electrodes. Whenever the circulation was stopped during the passage of the current, severe damage was done to the vessel wall. Structural alterations, however, were not produced when the blood was circulating freely. These observations suggested that it was the heat liberated in the obstructed vessel that was detrimental to the tissues of the vascular wall. It was thought that the free circulation prevented the overheating of the wall; hence no ill effect was caused by the current.

In order to confirm this explanation, we studied the effect of dry heat on the arterial wall. The femoral artery was prepared in the same



way as in the experiments with the electric current, and the surface was seared quickly with an aluminum steel wire, 3 mm. in thickness, which had been heated over a Bunsen burner until it started to glow and which then had been allowed to cool for thirty seconds. Touching the vessel with the hot wire caused a marked constriction, which lasted for about one minute. A microscopic examination of this vessel a week later showed changes which resembled very much those observed in the experiments with the electric current and the compressed lumen, except that they were more severe.



Fig. 2.—The femoral artery, experiment 9, in which the blood was left flowing freely during the passage of the electric current. The vessel shows no changes. The thickness of the media and the appearance of the internal elastic membrane should be noted. (Frozen section stained with hemalum eosin;  $\times 80$ .)

The lesions which were produced in the artery by the effective electric currents were as follows: Macroscopically, the exposed portion of the vessel was markedly distended and the wall was thin. It was so friable that often a slight handling with a forceps was sufficient to rupture it. Thrombosis was never observed, and in spite of the severe changes of the arterial wall, circulatory disturbances did not appear in the extremity supplied by it.

Under the microscope, the media was the part of the arterial wall that was most severely affected. It was compressed and only half as thick as in the normal artery (the reader may compare figs. 2 and 3). The nuclei of the muscle fibers of the media had disappeared as if they had been erased, and only a few shadow-like remnants were occasionally found near the internal elastic membrane (fig. 3). In the hemalum-eosin stained sections, the media took a uniform pale purplish-gray color; in the van Gieson preparations, it appeared pale yellow with a few purple wavy lines. The elastic tissue was less severely changed. It stained well

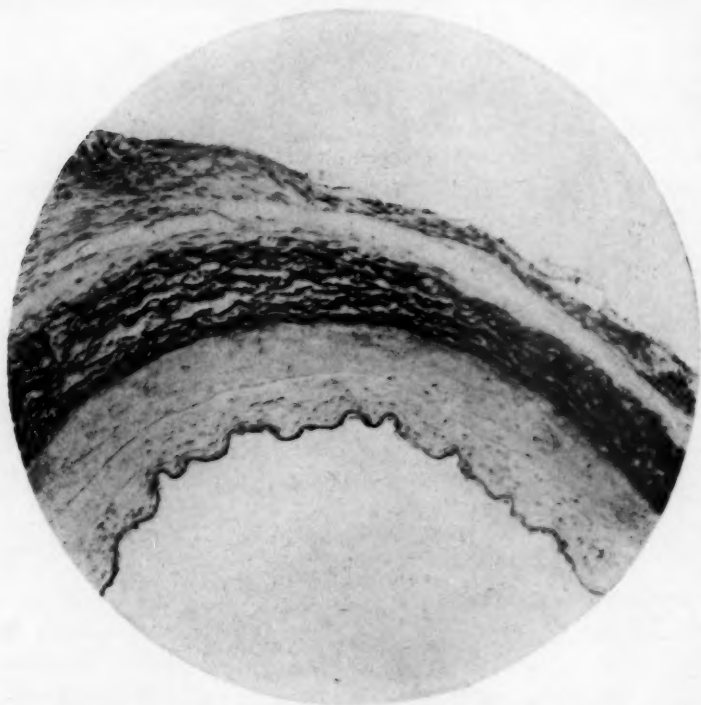


Fig. 3.—The artery, experiment 8, in which the flow of blood was stopped. The media is narrow and the lumen is wide. Pale-stained nuclear remnants are seen near the internal elastic membrane. Note the stretching of the internal elastic membrane. (Frozen section stained with hemalum eosin;  $\times 80$ .)

after Weigert, and in the media a system of branched and anastomosing fibers was seen, which differed from that of the normal artery only by the fibers being closer together. The internal elastic membrane, however, had lost its wavy appearance and was markedly stretched (fig. 4). In one experiment, the membrane remained almost unstained in the sections stained after Weigert's elastica method. In this experiment, the endothelial lining was completely gone, while in the vessels with

less extensive changes the endothelial cells still were visible. They sometimes appeared swollen, bulging into the lumen with large hyperchromatic nuclei. The adventitia showed little change. The elastic fibers were stretched but stained well, and the nuclei of the collagenous tissue were normal.

Examining the region of the electrodes, one saw that the dead and the living tissue bordered on each other directly, and a line of demarcation did not form within the period of observation, which was one week. Piling up of lipid material about the necrotic zone as it is observed,

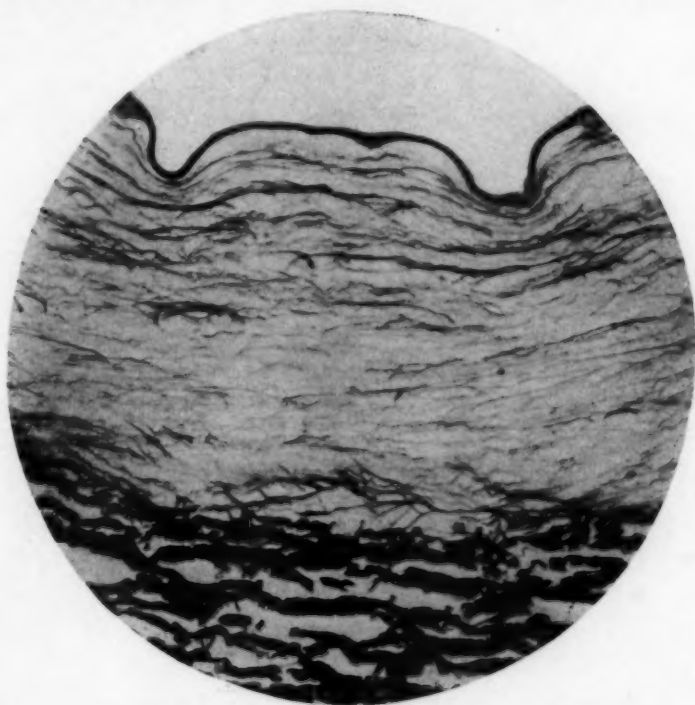


Fig. 4.—The artery, experiment 1. The internal elastic membrane is well stained but appears stretched. The media shows a network of elastic fibers, although the muscle fibers are gone. (Paraffin section prepared with Weigert's elastic stain and lithion carmine;  $\times 250$ .)

for instance, about anemic infarcts, was not seen. The necrosis did not stop in one level. In the outer third of the media, namely, it extended somewhat beyond the electrodes, and the borderline here ran circular (fig. 5). In this region, the intima was thickened and the endothelial cells proliferated, forming a gland-like lining.

In the seared blood vessels, the changes were similar. The wall was thin and friable, and the muscle fibers of the media had been destroyed.

The elastic tissue was more severely affected than by the electric current. In many places, it did not take the specific stains. The adventitia, too, showed marked regressive changes. Where the wire did not touch the vessel, the wall was found intact, and there was not any demarcation between the living and the necrotic portion.

Figure 5 illustrates these observations. In the lower half of the picture, one sees the wavy internal elastic membrane. In the upper half where the media is necrotic, the elastic membrane is flattened, and at a point higher up, not included in the photomicrograph, it has dis-

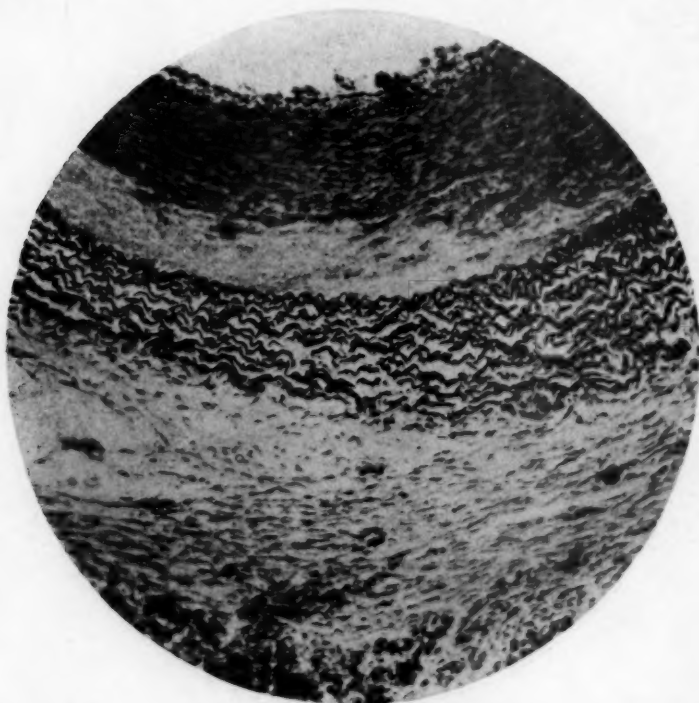


Fig. 5.—The artery, experiment 7, in which the circulation was stopped. This section is taken about 2 mm. distal from the electrode. The outer portion of the media is necrotic, while the internal layer shows little change. There is a slight thickening of the intima and a marked proliferation of the endothelium. (Frozen section stained with hemalum eosin;  $\times 80$ .)

appeared. In the media, a few elastic fibers can be made out. The intact portion of the elastic membrane is covered by an endothelial lining, the nuclei of which are distinct. Endothelial cells do not appear over the flattened portion.

It is evident from these observations that the differences between the lesions produced by the current and the lesions produced by the heat

were only gradual and that in places in which the action of the heat had been less intensive, as at the edges of the seared portion, the lesions were almost identical.

#### SUMMARY

As in the lesions of the skin, the changes that were produced in the arteries by the electric currents were nonspecific. They were due to the heat and could be duplicated by a slight searing of the vessel with a hot wire. Low tension currents were effective when their action was combined with a compression of the lumen of the artery. This observation,

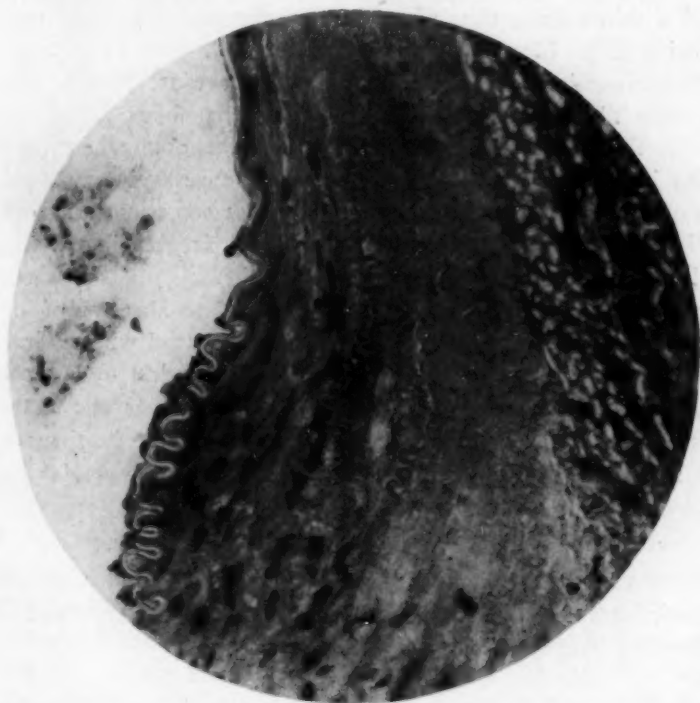


Fig. 6.—A section of a seared femoral artery. In the lowermost portion, the internal elastic membrane and the adjacent part of the media are not altered. Note how living and dead tissue border on each other without any line of demarcation. (Frozen section stained with hemalum eosin;  $\times 280$ .)

too, indicated that it was the thermic injury which destroyed the highest developed structures of the wall. With a free circulation of the blood, the wall of the vessel was cooled and thus an excessive temperature was prevented. In accidents with high tension currents, this cooling apparently is not sufficient, and the wall is destroyed in spite of the circulating blood.

The muscle fibers of the media were the most sensitive part of the wall. The elastic tissue was more resistant, retaining its staining prop-



erties but losing its elasticity. This was indicated by the stretching of the elastic membranes. Extremely high temperatures caused a complete destruction of all the elements of the wall.

Deprived of the essential structures that secured the firmness of the wall, the vessel became dilated and a fusiform aneurysm was formed. Spontaneous rupture of the injured arteries was not observed. It is remarkable that the vessels could stand the blood pressure with the media practically gone. After the experiments, the exposed artery was covered by the fascia and the wound was closed by a double layer of silk sutures. This precaution, and the luxurious granulation tissue that formed within a short time after the experiment, apparently prevented the forcing of the blood through the arterial wall.

The adventitia showed a high resistance against thermic injuries. The elastic fibers were stretched, but the collagenous tissue was not affected. The endothelial lining of the intima was gone where the media and the internal elastic membrane were most severely damaged. In places of less severe changes, the endothelium sometimes showed proliferation. There was no thrombosis, the blood circulated freely through the dilated segment of the artery.

An interesting observation was the complete absence of defense reactions. The necrotic segment fitted into the vessel without interruption of the continuity. It seems as if the heat had destroyed those substances of perhaps enzyme-like nature that, in tissue necrotic from other causes (such as lack of nutrition or toxins) stimulate its demarcation.

In a later publication, the final outcome of these vascular changes will be described.

#### CONCLUSION

The severe arterial changes that are frequently found in the vicinity of electric burns are due to the heat and are nonspecific for the action of the electric current.

# AORTIC LESIONS IN DOGS CAUSED BY INFECTION WITH SPIROCERCA SANGUINOLENTA \*

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NEW ORLEANS

Experimental Infection of Dogs with the Larvae

Macroscopic examination

Microscopic examination

General considerations

Natural Infection of Dogs with *Spirocera*

Macroscopic examination

Microscopic examination

General considerations

Comment

Conclusions

In 1922, one of us (Faust) found that the Asiatic hedgehog, *Erinaceus dealbatus*, taken in the vicinity of Peking, was infested with large numbers of larval nematodes, identified on morphologic grounds by Schwartz,<sup>1</sup> in 1926, as *Spirocera sanguinolenta*. These larvae were encysted in the tissues of the omentum and mesentery and on the peritoneal wall of the stomach and duodenum. During 1926 and 1927, Faust<sup>2</sup> fed these encysted larvae to dogs, cats and rabbits in an attempt to corroborate the morphologic diagnosis of the worm and to trace the route of migration through the tissues of the definitive host. The results showed clearly (1) that the dog was the natural mammalian host, although the early stages in the route of migration might be equally well observed in the cat, and (2) that the larvae after excystment in the stomach passed directly through the gastro-epiploic veins into the portal blood stream and thence by way of the capillaries of the liver and the lungs to the aorta, to which the worms became attached and in which they produced significant lesions.

The present paper embodies a study of the microscopic changes associated with these aortic lesions, undertaken with a view to determining

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1. Schwartz, B.: Parasitic Nematodes from China, Proc. U. S. Nat. Mus. **68**:1, 1926.

2. Faust, E. C.: Migration Route of *Spirocera Sanguinolenta* in Its Definitive Host, Proc. Soc. Exper. Biol. & Med. **25**:192, 1927.

the extent of the lesions and the course of migration of the worms through the aortic wall. In all, a series of fifteen dogs was used, of which seven were infected experimentally and the others naturally.

#### EXPERIMENTAL INFECTION WITH THE LARVAE OF SPIROCERCA SANGUINOLENTA IN DOGS

The puppies used for the series of experimental infections were born and reared in the laboratory. The technic employed in the work was similar to that described in a previous communication.<sup>2</sup> The period of incubation extended from four to thirty days.

#### MACROSCOPIC EXAMINATION

CASE 1.—The period of incubation was four days. The intima of the aorta from the arch to the seventh intercostal arteries was normal. From the latter level to the tenth intercostal arteries, just above the origin of the celiac axis, there were several worms attached to or embedded in the aortic wall, and lineal hemorrhages could be seen (fig. 1). Some of the worms lay partially free in the aortic lumen, but others were entirely buried in the aortic wall, just under the internal layer. The intima took on serpiginous elevations corresponding to the embedded worms. Furthermore, there were worms still free in the aortic lumen. The celiac artery showed similar lesions, but the mesenteric artery was not modified.

CASE 2.—The period of incubation was five days. The lineal hemorrhages were spread along the aortic intima from the fourth intercostal arteries to the celiac artery, and were more marked in the lower portion of the vessel (fig. 2). Several worms were found free in the aortic lumen, but more frequently they were attached to or buried in the aortic wall. The celiac artery showed similar changes, but the mesenteric artery was only slightly affected. The changes at this stage were similar to but more intensive than those in the earlier stage.

CASE 3.—The period of incubation was seven days. In the intima of the aorta, from its origin to the celiac artery, there were two types of changes, one of which consisted of the formation of nodules, the other of small dotlike hemorrhagic depressions. The nodules were arranged longitudinally, within 1 cm. of each other. The uppermost one was situated about 1 cm. from the common carotid artery. These nodules were each a little bigger than a pea, and in the natural state were whitish gray. The hemorrhagic depressions were usually scattered throughout the wall, between the fourth and seventh intercostal arteries. Many worms were attached to the lower part of the thoracic aorta and the upper part of the abdominal aorta.

CASE 4.—The period of incubation was eleven days. The aortic wall had a rough appearance throughout, from the posterior termination of the arch to the origin of the celiac artery (fig. 3). Many worms were buried in the aortic wall; only a few were free in the lumen. Hemorrhagic dots and lines were numerous. On the cut surface of the thickened media there were several small white dots within hemorrhagic areas.

The adventitia adhered to the surrounding tissue and showed a marked diffuse hemorrhage with numerous small white dots. The lesions along the thoracic aorta were somewhat more severe than those along the abdominal aorta. The celiac artery showed almost the same degree of modification, but the lesions on the mesenteric artery were less extensive.



Figure 1



Figure 2

Fig. 1.—The aorta of a puppy four days after the latter had been fed encysted third-stage larvae of *Spirocerca sanguinolenta*. The hemorrhagic linear tracts in the region of the abdominal aorta should be noted; natural size.

Fig. 2.—The aorta of a puppy five days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Linear hemorrhages in the region of the abdominal and posterior part of the aorta are to be noted; two-thirds natural size.



Figure 3



Figure 4

Fig. 3.—The aorta of a puppy eleven days after an experimental infection with the larvae of *Spirocera sanguinolenta*. Panarteritis purulenta is seen extending as far forward as the arch; two-thirds natural size.

Fig. 4.—The aorta of a puppy thirty days after an experimental infection with the larvae of *Spirocera sanguinolenta*. Tremendous fibrosis and the formation of nodules and aneurisms may be seen in the thoracic aorta, and a more or less normal appearance of the abdominal aorta; two-thirds natural size.



CASE 5.—The period of incubation was thirteen days. The aorta, from the posterior part of the arch to the commencement of the celiac artery, showed marked changes. The lesions were particularly prominent in the thoracic portion of the aorta. The inner aspect of this region appeared rough and irregular owing to numerous small elevations. Many of these were accompanied by hemorrhage. Moreover, in this region there were many blood-colored worms buried in the aortic wall. The corresponding adventitia adhered to the surrounding tissue and was invaded by many small white nodules and hemorrhagic areas. The abdominal portion of the aorta presented only a rough appearance, with numerous dotlike depressions over it.

CASE 6.—The period of incubation was fourteen days. The aorta throughout, from its origin in the thoracic region to the commencement of the celiac artery, was rough, owing to irregular thickenings; gross nodules, however, were not seen. The lesions were more severe in the thoracic portion of the aorta than at other levels. Worms were also found attached to and buried in the tissues.

CASE 7.—The period of incubation was thirty days. The aorta, from the posterior part of the arch to the commencement of the seventh intercostal arteries, was thickened as a whole (fig. 4). Throughout this region there were numerous small nodules, some of which were fused with their neighbors. The inner aspect of this portion of the vessel was extremely rough and irregular. The adventitia corresponding to this part adhered firmly to the surrounding tissue. In the cut surface of this tissue, worms were found that were apparently alive. Besides the thickening, small dotlike depressions without hemorrhage were seen throughout the aortic intima.

#### MICROSCOPIC EXAMINATION

CASE 1.—After an incubation of the larvae for four days, a section from the abdominal aorta, to which the worms were attached, was examined. The whole tissue was normal, except where the worms were embedded in the superficial layer of the media. Hemorrhage was not found in the immediate vicinity of the worms, but several small hemorrhagic foci were observed in places in which worms might have been previously situated. There was neither destruction of the media nor hemorrhage in the adventitia.

CASE 2.—After an incubation of the larvae for five days, a section from the abdominal aorta, in which the worms were embedded (fig. 5), was examined. Except for the worms embedded in the media, the tissues did not show changes. Some of the worms were lodged in the superficial layers of the media, others in the deeper layers. Hemorrhages were not seen around the worms, although small hemorrhagic areas were present in foci in which worms did not appear. In the adventitia there was an infiltration of many eosinophilic polymorphonuclear cells without hemorrhage.

CASE 3.—After an incubation of the larvae for seven days, a section from a nodule of the aorta was placed under the microscope. Except for the nodular part, it did not show any thickening of the intima. The nodule consisted of dense fibrous tissue, without elastic or muscle fibers. In the deeper part of the plaques, there were small capillaries, some of them containing red corpuscles. The most marked change was in the media. Just under the intimal plaques, the media was markedly destroyed, owing to fibroblastic growths. These fibroblasts were also seen in certain other areas. Some of them had broad connections with the adventitial connective tissue. The lamellar elastic fibers disappeared in the areas in which the fibroblastic growths were present. Therefore, the most marked

reduction in the elastic fibers was seen in the part just under the intimal plaques. In the fibroblastic growths, small capillaries were commonly present. Cellular infiltration was not particularly evident. The adventitial layer was without remarkable changes, except for an infiltration with eosinophilic polymorphonuclears and round cells, and a slight hemorrhage.

A section from the hepatic artery, in the wall of which the worms were embedded, was examined. Thickening or other change was not present in the intima. In the vicinity of the worms there was not any marked reaction in the media, but along the canal through which the worms had entered the tissue there were many wandering cells and round cells. There were some small areas

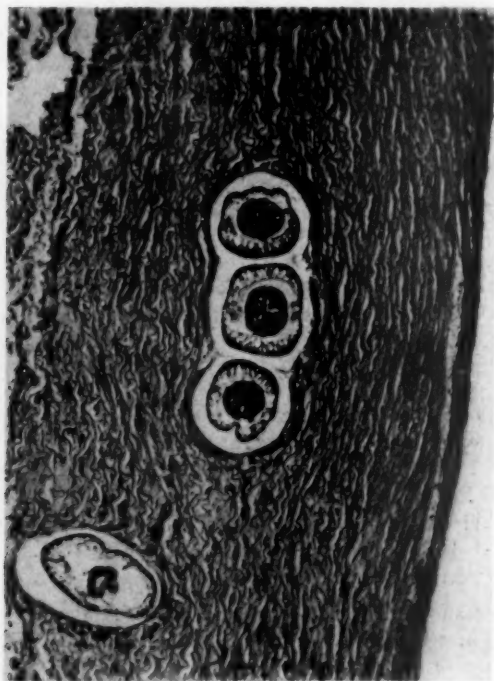


Fig. 5.—A section through the abdominal aorta of a puppy five days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. The worms may be seen embedded in the media. There are no marked changes in the tissues;  $\times 100$ .

in which the muscle fibers were necrotic and infiltrated with wandering cells and round cells. Infiltration with eosinophilic polymorphonuclear cells was common. The cellular infiltration was marked in the adventitia. Among these cells, eosinophils were the most numerous; hemorrhages were common.

CASE 4.—After an incubation of the larvae for eleven days, a section from the thoracic aorta (fig. 6) was examined. The intima was not thickened. The media was infiltrated with large numbers of eosinophils. In some regions, these cells were grouped together in local foci; in others, they were diffusely scattered throughout the media. In addition to the cellular infiltration, diffuse hemorrhage

was present. In the part adjacent to the adventitia, there were small newly formed capillaries derived from the adventitial layer. The formation of fibroblasts and small capillaries was marked in this layer, which was thickened throughout and hemorrhagic.

CASE 5.—After an incubation of the larvae for thirteen days, the aortic intima was edematous. Many polymorphonuclears and round cells were present. The former had infiltrated the media both in local foci and diffusely throughout the layers. Granulation tissue had developed markedly, having connection with the adventitia. Hemorrhages and worms were also found in the media. The adventitia was conspicuously infiltrated with polymorphonuclear cells. It showed a growth of granulation tissue.



Fig. 6.—A section through the thoracic aorta of a puppy eleven days after an experimental infection with the larvae of *Spirocerca sanguinolenta*. Cellular infiltration and diffuse hemorrhage in the media and fibrosis of the adventitia are to be noted;  $\times 100$ .

CASE 6.—After an incubation of the larvae for fourteen days, a section from the upper part of the thoracic aorta (fig. 7) was examined. The intima was slightly thickened, through the growth of dense fibrous layers. Corresponding to the marked destruction of the media, the intima was moderately thickened. Owing to the irregular growths of fibroblasts, the media was conspicuously destroyed, so that the normal arrangement of the media could scarcely be found, particularly of the part around embedded worms. On the other hand, the necrotic areas were infiltrated with polymorphonuclears, round cells and wandering cells. The destruction and resorption of the lamellar elastic fibers were

so complete that this portion of the media was hardly recognizable, and the boundary between the media and the adventitia was frequently obliterated.

There was marked cellular infiltration in the adventitia. The eosinophilic polymorphonuclear cells were the most abundant. Histiocytes and round cells were also present. Hemorrhage was common throughout the layer.

CASE 7.—After an incubation of the larvae for thirty days, a section from the upper part of the thoracic aorta was examined. The nodule consisted of dense fibrous layers and some muscle and elastic fibers in place of the normal intima. The myo-elastic layer appeared only inconspicuously in the deepest



Fig. 7.—A section through the upper part of the thoracic aorta of a puppy fourteen days after an infection with the larvae of *Spirocerca sanguinolenta*. Profound destruction and absorption of elastic and muscle fibers, leukocytic infiltration, diffuse hemorrhage and irregular fibroblastic replacement are seen;  $\times 100$ . Elastic-fiber staining.

portion of the nodule. The region of the media was noticeably thickened, while the normal tissues were profoundly altered. Fibroblastic areas, including small capillaries, as well as necrotic foci, were seen. Dead worms and small hemorrhagic lakes were also found. Cellular infiltration was fairly apparent throughout the entire media; eosinophils and round cells were common. The destruction and resorption of the lamellar elastic fibers were almost complete. The adventitia

was also conspicuously thickened. Fibroblastic growths were evident. Cellular infiltration was tremendous, the polymorphonuclear cells being the most abundant, and siderophilous cells numerous.

#### GENERAL CONSIDERATIONS

The aortic lesions were different in nature, in intensity and in localization, according to the length of the period of incubation. The experimental infection could be divided into three stages: the first, represented by the observations at four, five and seven days; the second, by those at eleven, thirteen and fourteen days, and the third by those at thirty days. The lesions consisted of hemorrhage, purulent inflammation and hypertrophy.

In the first stage, we saw only the worms embedded in the aortic wall, the areas of small localized hemorrhages that had occurred after the invasion of the worms and the infiltration of the adventitia with eosinophilic cells. The worms could be found only in the media, having more deeply invaded this layer in the five days' incubation than in the four days' incubation. Hemorrhage was present in the adventitia. The hemorrhage was lineal, and could be seen from the inner aspect only as a serpiginous line, as if it were a red-colored tracing on ivory. Later, it became diffused throughout the media and the adventitia, so that these coats were stained red. The lesions in the first stage (particularly at from four to five days after infection of the puppies) were localized mainly in the abdominal aorta near or anterior to the origin of the celiac axis, which was itself involved in the change.

Corresponding to the progress in the time of incubation, the lesions became more complicated and gradually extended toward the thoracic aorta. In the second and third stages, in contrast with the first stage, the significant lesions were situated at the thoracic level of the aorta. The most remarkable lesions in the second and third stages were the purulent inflammation and the hemorrhages in the media and the adventitia. The former occurred in both the diffuse and the localized types. The small white dots, which were observed macroscopically, were not other than foci of purulent inflammation. The localization and the size of these pustules were variable. But usually large purulent areas were not seen immediately beneath the endothelial layer. Hemorrhages of a rather diffuse type commonly occurred. In the adventitia, the granulation tissue consisted of fibroblasts and newly formed capillaries. These tissues were on the point of entering the media. Besides the growth of the granulation tissue, numerous eosinophils and hemorrhages were seen.

The lesions that have been described constitute a panarteritis purulenta. It is interesting to note, moreover, that this process was not found developing in the region in which the lesions of the first stage were most common, that is, in the abdominal aorta. The purulent



inflammation described was peculiar and different from that observed in cases of the infection in man, in that the infiltrated cells were mainly eosinophilic polymorphonuclear leukocytes.

In the third stage, the purulent foci had already been resorbed. Instead of pus pockets, there was localized granulation tissue. In these areas, the elastic and muscle fibers, for the most part, were destroyed and resorbed. The intima became thickened in the region corresponding to the destroyed media. The hemorrhage in the aortic wall had disappeared, but siderophilous cells were numerous in the adventitia.

It is now necessary to consider the way in which the worms invade and progress through the aortic wall. The larvae, once within the systemic circulation, gained entrance to the region of the thoracic and the upper part of the abdominal levels; we never found the lesions on the arch, the anteriorly directed arteries or the lower part of the abdominal aorta behind the celiac axis. Yet, in spite of the common presence of worms attached to the abdominal aorta in the early stage, the characteristic lesions, combined with the presence of the worms, were later found only on the thoracic aorta. If the worms that invaded the abdominal aorta penetrated outward, then there should have been adventitial hemorrhage and other profound reactionary lesions in this portion of the vessel. Such hemorrhages and inflammatory foci were not commonly found in the media of the abdominal aorta. For these reasons, we believe that the worms which entered the intima of the abdominal aorta soon migrated anteriorward toward the thoracic aorta, advancing within the middle coat. In support of this hypothesis is the arrangement of small dotlike depressions, which were more evident in the later stage when they were covered with an endothelial layer. The arrangement of these depressions was peculiar, that is, lineal and longitudinal to the aortic axis. It is altogether unlikely that the depressions indicated the points of entrance of part of the worms, since they were not combined with endothelial failure and hemorrhage. We suggest that these depressions may have been produced after the failure of the tissue of the superficial medial coat, caused by the advancing of the worms.

The further migration of the worms from the media to other layers is also an important point of investigation. We saw the worms embedded in the thickened adventitia during the second or third stage, but never during the first stage. Likewise, in the adventitia, in the second stage, purulent foci and hemorrhage were found, which without doubt were due to the worms rather than to micro-organisms, for we never saw purulent inflammation on the abdominal aorta. Some by-product of the worms was presumably responsible for this inflammatory process. Thus, we believe that the pus patches indicated former foci of the worms.

In spite of the fact that some of the worms embedded in the aortic wall undoubtedly died in situ (we saw the worm dead in the media during the third stage), we have substantial proof that the majority of the worms migrated out of the thoracic aorta during the second stage. From the facts mentioned, we may conclude that the penetration of the worms through the adventitia is certain.

#### NATURAL INFECTIONS WITH *SPIROCERCA* SANGUINOLENTA IN DOGS

In this study, eight dogs that were naturally infected with *Spirocerca* were examined. With the exception of one dog, which had been secured in Peking, all the others had been examined post mortem by one of us (Faust) in Amoy. The periods of incubation of the worms in these dogs were undoubtedly longer than the periods in the experimental cases. The dogs with the natural infections provided material that was particularly helpful in the study of lesions that had arisen from prolonged incubation.

#### MACROSCOPIC EXAMINATION

CASE 1.—With the exception of a few small dotlike depressions, the aortic arch did not show changes. On the thoracic aorta there were four depressed patches and one small nodule. One of these patches was deep and was the size of a pea; the others were shallow and narrowly elliptic. The margins of these latter depressions were whitish gray and were slightly elevated. On the abdominal aorta, a few small dotlike depressions were found.

CASE 2.—The changes in this case were relatively simple: that is, two nodules and numerous small dotlike depressions. The two nodules were situated on the thoracic aorta. One of these measured about 10 mm. in diameter. The other was smaller, being about 7 mm. in diameter. Both nodules were whitish gray. The small dotlike depressions were distributed in considerable numbers from the upper part of the thoracic aorta to the abdominal aorta.

CASE 3.—On the thoracic aorta and the upper part of the abdominal aorta several small nodules and depressed patches were noted. These depressions were each about the size of a rice grain. The small dotlike depressions were numerous and were distributed throughout the thoracic and the abdominal aorta.

CASE 4 (fig. 8).—The thoracic aorta was profoundly modified, showing a closely arranged pattern of many depressions, each about 10 mm. in diameter. The aortic wall at this level was distended and much thinner than it was in the other parts. Besides the larger depressions, a few elevated patches were seen along the vessel.

CASE 5.—On the lower part of the thoracic aorta there were three depressed patches. Two of them were shallow and were each about the size of a pea. The other was bigger, being the size of a broad-bean, and had a deep thin wall. Small dotlike depressions were distributed along the lower part of the thoracic aorta and the upper part of the abdominal aorta.



Fig. 8.—The thoracic aorta and the adjacent portion of the esophagus of a dog that has been naturally infected with *Spirocera sanguinolenta*. The nodules and the aneurisms in the wall of the aorta and the large nodules in the esophageal wall are to be noted. The adult worms live in the latter nodules; natural size.

CASE 6.—On the lower part of the thoracic aorta there were three depressions, each about the size of a pea. Small dotlike depressions were numerous on the lower part of the thoracic aorta and the upper part of the abdominal aorta.

CASE 7 (fig. 9).—The lesions in this case were marked throughout the entire thoracic aorta. Adjacent to the arch there were several small depressions. Their margins were slightly thickened. From this region to the sixth intercostal arteries, there were several small depressions. The inner aspect of this region had an



Fig. 9.—The thoracic aorta of a dog that has been naturally infected with *Spirocerca sanguinolenta*. It shows the formation of nodules and aneurisms and an adjacent uninfested portion of the esophagus; natural size.

extremely irregular appearance. Besides these depressions, one nodule was seen on the upper part of the thoracic aorta, with a diameter of about 10 mm. Small dotlike depressions were commonly distributed throughout the wall of the vessel.

CASE 8.—On the lower part of the thoracic aorta and the upper part of the abdominal aorta, there were marked changes consisting of closely arranged nodules and large and small dotlike depressions. However, these nodules and depressions were all rather small as compared with those observed in the other members of the series. The inner aspect of the wall appeared rough and irregular.

## MICROSCOPIC EXAMINATION

CASE 1.—A section from the aneurismic cavity was examined. The boundary between the intima and the media could not be seen. The elastic fibers were almost completely resorbed, and had been replaced by dense lamellate fibrotic layers. Although muscle fibers were to be seen more commonly toward the inner surface than on the outer side, there was a marked reduction from the normal number. In the adventitia, we saw numerous siderophilous cells. Cellular infiltration was not evident.

CASE 2.—Sections from a nodular portion were examined. A boundary between the intima and the media, in the part corresponding to the most elevated



Fig. 10.—A section from an aneurismic cavity of the thoracic aorta of a naturally infected dog (case 4), showing enormous thickening, the destruction of elastic and muscular fibers, and their replacement by dense fibrotic and fibroblastic growths;  $\times 43$ .

part of the nodule, could not be found. This part consisted mostly of dense fibrotic layers without any elastic and muscle fibers. In certain regions, the dense fibrotic layers had a tissue connection with the adventitial fibrotic layers. In the depth of the nodule, we saw a marked localized cellular infiltration. Among the infiltrated cells, the histiocytes and fibroblasts were the most numerous, although small round cells and polymorphonuclear cells were also numerous.

The intima adjacent to the nodule was slightly thickened, and consisted of elastic and muscle fibers. In the media of these parts, dense fibrotic layers arose continuously from the nodular area. Siderophilous cells were commonly observed in the adventitia.



CASE 3.—Sections from the slit-shaped depressions were examined. The intima was moderately thickened, owing to the growth of the elastic, muscular and fibrotic tissues in areas in which the media showed more or less marked lesions. Around the margin of the depression, the media was destroyed by dense fibrotic and fibroblastic growths, so that we did not see elastic and muscle fibers in this region. The other parts of the media did not indicate any marked change. Cellular infiltration was seen only in the fibroblastic layer. Siderophilous cells were also present in the adventitia.

CASE 4.—Serial sections from the aneurismic cavity (fig. 10) were examined. The intima was enormously thickened. In the corresponding media, traces of the ordinary structure of the media were not found. This region consisted, as a whole, of dense fibrotic and fibroblastic growths. The outermost layer of this thickening seemed to be compressed from the inside and showed a firm appearance.

Adjacent to this cavity there was neither thickening of the intima nor modification of the media. The margin of the cavity was elevated slightly throughout the fibrotic layer. Worms could not be found. Siderophilous cells were present in the adventitia.

CASE 5.—Sections from the large aneurismic cavity were examined. The intima was moderately thickened, owing to the growth of fibrotic and muscle elements mingled with small amounts of elastic fibers. At the bottom of the cavity, the boundary between the media and the intima had disappeared, and a large amount of bone with bone-marrow was to be seen. The dense fibrotic layers had grown measurably at the expense of the elastic and muscle fibers. Where the media did not show lesions, the intima was not modified. There were extremely few siderophilous cells in the adventitia. Infiltration of this layer with cells was not observed.

CASE 6.—Sections from the aneurismic cavity were examined. The boundary between the intima and the media was obscured. This region consisted mainly of a dense fibrotic layer, containing bone tissue with bone-marrow. Elastic and muscle fibers were not seen. Round cells were moderately common, and small capillaries were visible. Owing to fibrotic growth, there was thickening of the intima adjacent to the margin of the cavity. In the adventitia, there were numerous siderophilous cells.

CASE 7.—Serial sections from the nodular portion (fig. 11) were examined. The nodule consisted of densely fibrosed layers of intima. The boundary between the intima and the media in the nodular part was already obscure, and the corresponding part of the media consisted of fibrotic or fibroblastic growths instead of muscle and elastic fibers. The dense fibrotic tissue in some areas had changed into hyaline or cartilaginous tissue; furthermore, we saw bone tissue in the depth of the nodule.

Adjacent to the nodule, the intima was thickened more or less, through fibrotic or fibroblastic growths. Not far from the nodule, however, no thickening was present. The lesions in the media corresponded in position rather closely with the intimal thickening; that is, the most marked lesions were seen where the intima was most noticeably thickened. Small capillaries were seen everywhere throughout the whole of the media, but cellular infiltration was not noticeable. Siderophilous cells were found in the adventitia.

Worms could not be found in any of the sections.

Serial sections from the small slit-shaped depression were examined. The intima was thickened throughout by dense fibrotic and fibroblastic growths. The inner surfaces of this depressed intimal thickening showed marked irregu-

larities. The boundary between the intima and the media was not visible. The margin of the depression was slightly elevated.

Worms were not found anywhere in the sections. Siderophilous cells were present in the adventitia.

CASE 8.—Sections from the shallow depression were examined. The intima was slightly thickened. The media of this region consisted of dense fibrotic and fibroblastic growths, and was thickened to about twice its normal size. This medial thickening extended mostly outward. In the adventitia and the surrounding tissue, many siderophilous cells were seen.



Fig. 11.—A section through a nodular portion of the thoracic aorta of a naturally infected dog (case 7), showing formation of bone;  $\times 100$ .

#### GENERAL CONSIDERATIONS

The lesions in the cases of natural infection could be divided into three main groups: small dotlike depressions, nodules and depressed "holes." The depressed "holes" were really small localized aneurisms, the depressions having been produced by the expansion of the aortic wall at a particular location. These small aneurisms, of course, did not occupy the entire circumference of the aortic wall, and each usually constituted only a saccular diverticulum. But if these aneurisms in large

numbers were situated close to one another, then the aortic wall expanded as a whole. A good example of this was found in case 4.

The small aneurisms could be divided into two types. One was slit-shaped; the other looked as if it had been produced by pressure of the finger. Some of the slit-shaped depressions had consistently thickened margins, but others did not. The thickened margin appeared similar to that of the nodule. The other type of aneurism did not have a thickened margin; it consisted only of a diverticular sac of the aortic wall, the thinness of the wall being indirectly proportional to the size of the sac.

The nodules were whitish gray and never yellowish. The smallest nodule was the size of a white bean; the largest about that of a broad-bean. Their consistency was always hard. With the exception of those in case 8, the aneurisms and the nodules were found consistently on the thoracic aorta. The small dotlike depressions were distributed throughout the thoracic and the abdominal aorta, arranged somewhat in a linear pattern. It is interesting that the small depressions could be seen commonly on the abdominal aorta, particularly on the portion adjacent to the celiac axis, although on this part the nodules and the aneurisms were never seen. The lesions were situated, for the most part, on the back wall of the aorta.

The most marked change in this series was the destruction of the media. In both the nodular and the aneurismic portions, the media was destroyed in the same manner, namely, by the resorption and replacement of muscle and elastic fibers. Instead of these fibers there were growths of dense fibrotic and fibroblastic tissue. We never saw the boundary between the intima and the media in these parts. The amount of intimal thickening could be easily appreciated by comparison with the adjacent normal intima, even though the boundary between the intima and the media was indefinite. Thickening of the intima was not seen except in those regions in which there was destruction of the media. The fibrotic and fibroblastic growths usually broke out in localized patches.

These growths developed somewhat differently on the nodule and in the aneurismic cavity. In the region of the nodule, they produced a thickening of the media; in the aneurismic cavity, they became denser and rather decreased in thickness. Small capillaries and cellular infiltration were always found in the media, although at times they were not conspicuous. Besides these lesions, we saw osteoblasts in the media; some of them even had bone-marrow. The adventitia was usually thickened, more or less, by means of fibrotic growths. We did not find hemorrhage, but always found numerous siderophilous cells. In spite of careful examination through the several sections, we could not find traces of worms in any part of the aortic wall.

It is desirable at this point to compare the nodular type with the aneurismic type of lesion. For convenience, their relative frequency in this series is set down in the accompanying table.

These cases may be naturally divided into three groups: (1) those in which there was building of the nodule, without aneurismic cavities (case 2); (2) those in which there was building of aneurismic cavities without nodules (cases 3, 4, 5 and 6), and (3) those in which there was building of both nodules and aneurismic cavities (cases 1, 2, 7 and 8).

As previously mentioned, the histologic changes represented in the nodular and aneurismic lesions were similar, with this difference, that

*Comparative Frequency of Nodules, Aneurismic Cavities and Dotlike Depressions in Cases of Natural Infections with Spirocerca in Dogs*

Case	Nodule	Aneurismic Cavities	Dotlike Depressions
1	One, small.....	Four, one of which was the size of a pea; the others, small and shallow	Common
2	Two, one of which was the size of a small finger-tip; another, the size of a bean	None.....	Very common
3	None.....	Several, slit-shaped, not large and deep	Very common
4	None.....	Many, each the size of a small finger-tip	Common
5	None.....	Three, the largest the size of a broad-bean, and the others, each the size of a pea	Very common
6	None.....	Three, each little bigger than a pea	Very common
7	Several, one of which was the size of a small finger-tip; the others, all small	Several, small and shallow, slit-shaped	Very common
8	Several, the largest of which was the size of a bean	Two, small and shallow.....	Very common

the fibrotic layer of the aneurismic media was denser. It seems probable that the aneurismic cavity replaced the nodule. We called attention to the slit-shaped depressions with thickened margins. These constituted an intermediate stage between the nodule and the aneurismic diverticulum. Accordingly, the case which had an aneurismic cavity was older than the case which had the nodule alone. Thus, we may conclude that the period of incubation was shortest in the first group, and longest in the second group, while in the third it was intermediate. With few exceptions, these lesions were always situated on the thoracic aorta.

Although worms were not seen in these lesions and although the formation of giant cells was not observed, siderophilous cells, which were commonly present in the adventitia, were indicative of previous hemorrhage in that issue. For these reasons, we may conclude that the worms that caused the aortic lesions had already penetrated the aortic wall.



## COMMENT

As far as we are aware, the aortic lesions produced by *Spirocerca sanguinolenta* in the dog are not duplicated by any other infection in this host. Comparable infestations with nematodes in water buffaloes and in cattle in the Dutch East Indies and in Annam (*Filaria poeli* Vryburg, 1897), and those in cattle in Annam and Senegal (*Onchocerca armillata* Railliet and Henry, 1909) produced almost identical lesions, with hypertrophy of the intima, dissociation of the elastic fibers, and destruction of the muscular elements with formation of osteoblasts, but without as marked changes in the adventitia—the gross picture being that of a formation of nodules leading to the development of aneurisms along the wall of the aorta (Bernard and Bauche,<sup>3</sup> Commes and Devanille<sup>4</sup>). Essentially similar changes were produced in the ileocecolic artery in horses by species of the nematode genus *Sclerostoma* (Adelmann<sup>5</sup>). In all these infections, the adult worms were found in the wall of the digestive tract at a level corresponding to the level of the aortic lesions.

In bovine and equine species, the pathologic processes have been studied only after the worms have migrated out of the arterial wall and have become lodged in the wall of the digestive tract. The earlier stages of this type of verminous infection, including the method of attachment to and invasion of the aortic wall, the passage of the worms into the media and the concomitant changes of the tissues involved, are here described for the first time. It seems altogether likely, however, that a similar course is pursued by the nematode parasites producing aortic lesions in cattle and horses.

Atheromas of the aorta in man, leading to the formation of aneurisms are, for the most part, syphilitic in origin. While the gross alterations of the aorta are similar to those produced by *Spirocerca sanguinolenta* in dogs, the presence of granulation tissue (gummas) and giant cells, and the absence of eosinophils and of osteoblasts, as well as the usually demonstrable presence of the organism *Spirocheta pallida* in the tissues, all serve to distinguish these two types of lesions. Syphilitic aneurism also occurs higher on the arch than does verminous aneurism.

A perforation of the weakened dilated portions of the aortic wall was not recorded for any of the members of the experimental series reported in this paper. However, in an earlier series, which was used for tracing the route of migration of the larvae of *Spirocerca* from the lumen of the stomach to the aortic wall (Faust<sup>2</sup>), death of one host

3. Bernard, P. N., and Bauche, J.: Filariose et atherome aortique du buffle et du boeuf, Bull. Soc. de path. exot. **5**:109, 1912.

4. Commes, Charles, and Devanille, P.: L'onchocercose aortique bovine dans le Haut-Senegal-Niger, Bull. Soc. de path. exot. **10**:459, 1917.

5. Adelmann, F.: Das Aneurysma verminosum equi, Berlin, L. Schumacher, 1908.



from perforation of the aorta just behind the arch occurred fourteen days after the feeding of the cysts, the perforation most probably being caused by the actively penetrating advanced third-stage larva that was found attached to the adventitia near the point of perforation. Other animals on which autopsies were made at from nine to thirty days following infection, had lesions so deep that only a thin layer of the adventitia remained unperforated. In general, it was noted that this more rapid acute termination of the infection resulted when the larvae were more mature and consequently larger at the time that they were fed to the host. Likewise, the delicate aortic wall of puppies was more likely to be perforated rapidly than was the thicker one of the adult dog. Perforation in the case of advanced chronic lesions in naturally infected animals due to gradual weakening of the wall at the site of the formation of a nodule or of an aneurism also occurred not infrequently and resulted in fatal hemorrhage.

#### CONCLUSIONS

The mature third-stage larvae of *Spirocerca sanguinolenta* can be found in the aortic wall for the first time about four days after the feeding of cysts. The majority of the worms are found at about the twelfth or the thirteenth day.

The larvae first attack the abdominal aorta, but later on the majority of the worms can be found in the thoracic portion of the vessel. The worms advance within the aortic wall from the abdominal to the thoracic aorta. Probably, also, some of the larvae attack and penetrate the thoracic aorta directly.

The changes produced by the worms in the earliest stage are hemorrhage and purulent inflammation. This inflammation seems not to be due to secondary micro-organisms, but to by-products of the worms. It is not as intensive a process in the thoracic as in the abdominal aorta.

The larvae penetrate through the tissue of the aortic wall in the thoracic region. While the majority of the worms probably migrate out of the aorta to the adjacent portion of the intestinal tract, some of them die in the aortic wall.

The lesions that have been found in naturally infected dogs are a succession of changes of purulent inflammation of the aortic wall, with a destruction of muscle and elastic elements and a replacement of these elements with growths of dense fibrotic and fibroblastic tissue.

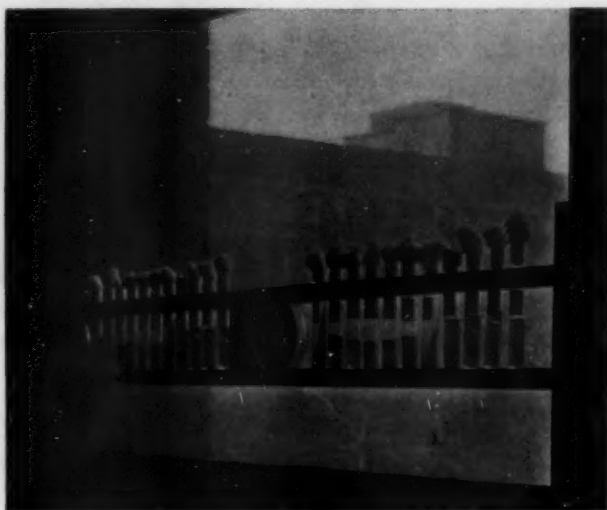
The advanced aortic lesions in naturally infected dogs are directly comparable with the verminous lesions of the aorta in cattle and water-buffaloes and with those of the ileoceocolic artery in horses. The earlier lesions are described here for the first time.

## Laboratory Methods and Technical Notes

### WINDOW DEMONSTRATION IN TEACHING BACTERIOLOGY\*

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The teaching of medical bacteriology requires not only didactic methods for the purpose of correlating laboratory work with clinical medicine, but also an efficient, time-saving arrangement of demonstrations and laboratory work by the students. Since the student's time in the laboratory is limited and the bacteriologic characteristics of organisms have little clinical application, in many medical schools instruction in the practical routine of hospital and public health examinations has replaced, in large measure, the study of organisms as outlined in the descriptive chart. The window demonstration offers a partial solution of the problem of retaining certain favorable features of the older methods of teaching bacteriology while entailing a minimal expenditure of time on the part of the student.



Wooden frames, similar to gigantic test tube racks, consisting chiefly of two horizontal strips, as shown in the accompanying figure, are built across classroom windows, which are readily accessible to the students. The racks hold culture tubes and plates containing the various mediums designated in the descriptive chart, and, in addition, have space for special demonstrations.

The laboratory work on a particular organism or group of organisms in the class room is confined chiefly to diagnostic procedures or problems. In addition, the students are furnished with pure cultures for microscopic examination. From the window demonstrations, the macroscopic growth and biologic characteristics of the bacteria on the various mediums may be recorded by the students on a modified descriptive chart without any appreciable loss of time, at any convenient opportunity during the laboratory period.

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## General Review

### TRAUMA AND TUMORS\*

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The consideration of a single trauma as either the direct exciting cause or one of the contributory causes of a neoplasm recurs in medical literature from time to time because it possesses several interesting aspects, no one of which has ever been thoroughly understood. At an early period, beginning with 1870, many pathologists were led to serious scrutiny of the subject because of a widespread interest in the etiology of tumors, especially after the publication in 1868 of Virchow's<sup>1</sup> theory of chronic irritation. With the publication in 1877 of Cohnheim's theory of embryonic remnants, and with the development of new methods of microscopic technic and of bacteriologic and immunologic investigation, beginning with Pasteur in 1880, inquiry was begun into all the factors of possible importance in tumor causation. Then began an attempted evaluation of the importance of both single and repeated mechanical traumas. This early period of investigation covers the years between 1870 and 1880, during which several papers appeared, none, however, of any particular ultimate value.

Fresh interest in the subject arose after 1900, and especially during the subsequent decade, although scarcely a year has passed since without some serious renewal of the discussion. This recent period coincides not so much with the theoretical interest in the etiology of tumors as with the increasing legal responsibilities of employers to employees and the increasing claims made by the latter for compensation for disability resulting from injuries. During the last fifteen years, this practical aspect of the subject has again led to a demand for the solution of the problem of the traumatic factor in tumor. Many judicial opinions which are available in such texts as Engel's<sup>2</sup> and Löwenstein's<sup>3</sup> have not always been brought to the attention of the American medical and legal authorities.

\* Submitted for publication, June 1, 1928.

\* From St. Luke's Hospital.

1. Virchow, R.: *Die Krankhaften Geschwülste*, Berlin, 1863, p. 35. Lubarsch: *Die Virchowsche Geschwülstlehre und ihre Weiterentwicklung*, *Virchows Arch. f. path. Anat.* **235**:235, 1921.

2. Engel, H.: *Die Beurteilung von Unfallfolgen*, Berlin, 1913, p. 340.

3. Löwenstein, S.: *Ueber Unfall und Krebskrankheit*, Tübingen, 1910 (bibliography); also *Beitr. z. klin. Chir.* **69**:533, 1910; **69**:693, 1910; **74**:715, 1911, and **76**:750, 1911.

The present paper is concerned, therefore, with presenting a résumé of the literature on the relationship between trauma and the production of a tumor, especially of those papers which have extended beyond a mere compilation of the statements of patients' opinions.<sup>4</sup>

The various decisions made in this country under the workingmen's compensation laws have been frequently rendered without regard to the scientific aspects of the questions at issue; and both legal and medical opinions are often expressed without a clear conception of the nature of the evidence or an accurate knowledge of the facts on which the opinions are based.

Present day thought finds it almost impossible to regard any one agent as the sole cause of a disease, even a disease of so limited a type as cancer. This point Gaylord, von Hansemann<sup>5</sup> and Ewing<sup>6</sup> in their reviews of the subject frequently stressed. Even in the infectious diseases, heredity, constitutional predisposition and other contributory causes are so generally implicated that a single indispensable exciting agent is readily questioned. Tuberculosis, for example, is believed to be so intimately associated with environmental, nutritional and hygienic factors that the bacillus of Koch does not perhaps always receive its just share of blame. And so, in the case of tumors, one inclines to involve several factors—chronic irritation, possibly an inherited predisposition, degenerative lesions, physiologic changes and the wear and tear of bodily activity. It is this tendency to seek for multiple causes which has led some writers to consider a single trauma and its resulting reparative and exudative processes to be a special and directly exciting cause of tumor. This notion is still firmly fixed in the lay mind, but with the great increase in precise knowledge of the proximate cause of cancer, as experimentally demonstrated in the past decade, the attitude of the student of cancer has changed. The tar cancer of mice and rabbits discovered by the Japanese, the gastric cancer of rats shown by Fibiger to be due to a nematode, the sarcoma of the liver in rats produced on a

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4. It is obviously impossible to record here within reasonable limits the clinical histories of the thousands of cases of tumors alleged to have been produced by traumas. A few cases have been selected out of a vast number, some to illustrate the lack of logic which characterizes many of the case reports; and others to record cases which have been carefully observed and in which, if ever, the possibility of the production of the tumor is recorded. The bibliography, which has been carefully verified, offers to any one who wishes to read the detailed records, an opportunity to consult them. Much of what has been published is utterly unprofitable to read. Statistical elaboration of a thousand such incorrect histories would not furnish facts of value. The stream cannot rise higher than its source.

5. Von Hansemann: *Ztschr. f. Krebsforsch.* 15:492, 1916.

6. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.



large scale by Bullock and Curtis, the x-ray cancer in man, have led the majority of the oncologists rather to incriminate more and more some type of chronic irritative process as the only known inciting agent of cancer and to doubt the efficacy of a single trauma in the direct production of a malignant neoplasm. It has never been possible to produce a malignant growth experimentally in animals by a single trauma.

The present discussion is restricted so far as possible to a survey of the cases of tumor believed to have been caused by a single trauma as opposed to cases caused by repeated chronic irritation of a mechanical or chemical type. The latter have been extensively studied by numerous cancer research workers, and have been found to have little relation, in any case, to the effects of a single injury. These two groups of cases can, perhaps, never be entirely separated because many of the tumors ascribed to single injuries have arisen each on the basis of a scar of many years' duration, which originally was caused, no doubt, by a single laceration, blow or contusion. On closer examination, however, it is to be noted that many a scar, although incited by one such agent, has continued as a demonstrable lesion over a period of years because of the presence of foreign material which was implanted in the beginning, or possibly because of a prolonged infection. It is generally accepted that keloids and other hypertrophic scars often contain some foreign material, even if racial and individual reparative processes add complicating factors. One of the best known facts in medicine is that tissues have the capacity to heal completely and the scar to atrophy in the course of a year or two. The tissues then become so nearly normal, if foreign bodies are not present and there has not been any gross disturbance of the circulation, that a tumor arising in an atrophic scar cannot be understood to bear any relation to the preceding injury.

Nearly all the literature purporting to prove that tumors are directly caused by single traumas includes, also, as traumatic causes, the chronic inflammatory diseases, such as mastitis and chronic cervicitis, and the ulceration produced by parasites and chemicals. It is well known, however, that all of these require continuous applications of the irritants for long periods, throughout which not only one but many stimuli are added. These, therefore, are entirely excluded from the present consideration. Their etiologic importance has been repeatedly and accurately discussed in the literature dealing with tumors, because these phases of the subject are of interest to the scientific mind because experimentally demonstrable, whereas the etiologic importance of single trauma is no longer a matter of genuine interest to this group, partially because the subject was discarded years ago by many of the great leaders in pathology after careful research had been carried out. It has been revived, not by the scientific group, but by commercial interests, because



of the increasing accessibility of compensation for any injuries sustained while in the discharge of any kind of employment, especially if the presence of a tumor in an employee gives countenance to the idea that it may have had a traumatic origin.

#### EXPERIMENTAL RESEARCH

A large amount of experimental work was done by Lubarsch,<sup>7</sup> Ribbert<sup>8</sup> and others. That of Lubarsch was perhaps the most intelligent. He utilized many series of animals, the tissues and tumors of which he traumatized in the hope of ascertaining what effect mechanical forces could exert on the rate of growth of normal or neoplastic tissues. He inoculated sarcoma into mice and rats and also traumatized spontaneous fibroadenomas of the breast in rats and epitheliomas of the dog for a minute at a time with a percussion hammer. He also crushed these growths with forceps, and injected homologous and foreign blood over a period of weeks or months, but he did not observe any increase in the rate of the growth of the tumors. The breast tumors were unchanged morphologically, and the mitotic figures were not increased. In mice that had two tumors, the traumatized one at times regressed or remained the same size, while the other grew. It was Lubarsch's conclusion that trauma could be accepted as a factor in growth only if (a) the violence was severe, was localized and caused long continued injury at the same point as that at which the tumor later appeared, and also if (b) the histologic structure of such a tumor made it appear reasonable that the growth was due to the injury. He found no regressive effect unless the blood supply was cut off. There are, however, recorded examples of human tumors which receded for long periods after partial excision.

Ribbert also investigated this subject and performed many implantation experiments in the attempt to produce epitheliomas. His experiments were motivated by the work of Cohnheim and if malignant tumors had resulted the work would probably have greatly strengthened Cohnheim's hypothesis as to the etiologic importance of misplaced embryonal rests. Such experiments with great uniformity led only to discouraging results, as an implantation dermoid cyst appeared to be the only tumor which he could produce with any regularity. Absolutely no malignant tumors resulted.

Barfurth<sup>9</sup> also attempted to produce tumors by mechanically displacing the cells of sea urchin's eggs in the gastrula stage, but instead of tumors, he formed only simple dermoid cysts. Traumatized tissues, both embryonic and adult, have been repeatedly introduced into animals

7. Lubarsch: *Med. Klin.* 8:1651, 1912.

8. Ribbert: *Deutsche Ztschr. f. Chir.* 47:574, 1898.

9. Barfurth, Merkel-Bonnet: *Anatomische Hefte*, 1893, sect. 1, no. 9.

by Zahn<sup>10</sup> and many others. Fetal cartilage and bone were implanted by Zahn under the capsule of the kidney. Birch-Hirschfeld and Garten<sup>11</sup> injected embryonal tissue into the vena cava of animals. This produced growths in both the liver and the lungs for a short time, but these eventually receded and tumors were never produced. Nichols<sup>12</sup> inoculated rabbits and guinea-pigs with cells of various organs but failed to obtain malignant growths. Only Askanazy<sup>13</sup> and Carrel<sup>14</sup> succeeded in producing malignant tumors in the rat and fowl, respectively, by injection of embryonic material plus minute quantities of arsenic. Obviously, these results with embryonic tissue did not have anything to do with the question of producing tumors by traumatic injury of adult cells.

Cohnheim and Maas<sup>15</sup> and Fischer<sup>16</sup> also tried to form bony tumors by introducing periosteum and cartilage into veins, but without success. Leopold<sup>17</sup> implanted cartilage subcutaneously, also without results. Gland grafts likewise were done in great numbers and often succeeded temporarily, but tumors did not result.

It is unnecessary to cite further examples of this type. The most recent bibliography of bone grafting is in a paper by De Jong and van der Kemp.<sup>18</sup> If such grafting of foreign cells in normal tissues really produced neoplasms, every patient undergoing an osteoplastic operation would be in grave danger.

Slye<sup>19</sup> described eighty-seven sarcomas in mice, in eleven of which the tumor was believed to have arisen at the site of a previous injury. In these cases, either the locality of the injury was noted and it was observed that afterward a sarcoma made its appearance at this point or a tumor was observed at the site of a scar from some old injury. Proof was not offered that any of these sarcomas were directly produced by the traumas (bites), and experiments were not done to show the susceptibility of the strains studied to a type of injury which might produce a tumor without an intermediary process such as chronic inflammation or scar production. In the rats, an animal in which sarcoma is the most frequent type of tumor, sarcoma formation was not observed to

10. Zahn: Virchows Arch. f. path. Anat. **95**:369, 1884.

11. Birch-Hirschfeld and Garten: Beitr. z. path. Anat. u. z. allg. Path. **26**:132, 1899 (bibl.).

12. Nichols: J. M. Research, n. s. **8**:221, 1904.

13. Askanazy: Verhandl. d. deutsch. path. Gesellsch. **21**:182, 1926.

14. Carrel, A.: Compt. rend. Soc. de biol. **93**:1083, 1925.

15. Cohnheim and Maas: Virchows Arch. f. path. Anat. **70**:161, 1877.

16. Fischer: Deutsche Ztschr. f. Chir. **17**:61 and 362, 1882.

17. Leopold, G.: Virchows Arch. f. path. Anat. **85**:283, 1881.

18. DeJong and van der Kemp: Beitr. z. path. Anat. u. z. allg. Path. **79**:268, 1928.

19. Slye, Holmes and Wells: J. Cancer Research **2**:1, 1917.

follow bites in a large series of animals under close observation. Both species of rodents frequently bite their cage mates, and yet superficial tumors are rare (Curtis<sup>20</sup>).

#### CLINICAL OBSERVATIONS

Aside from such experimental work, it must be realized that the only other available material on which to base conclusions is compilations of case histories. Early it was observed by Schimmelbusch<sup>21</sup> that such material as this rendered any conclusion impossible because scientific matters could not be decided on the basis of unreliable and untrustworthy evidence and that, on this subject, all the evidence is essentially unreliable. Askanazy<sup>22</sup> stated that the literature dealing with the subject was only a "collection of anecdotes" and that there were many highly uncritical studies in the literature. This seemed so important a verdict to many that in 1909 a set of postulates were expressed by Thiem<sup>23</sup> in the hope of directing attention to the need for soundness in analysis of case records and to the unreliable character of much material hitherto accepted as valid.

The clinical evidence may therefore be divided into two classes: one embracing the large tabulation of histories drawn from hundreds of hospital records, all used as evidence without regard to the honesty, the mental capacity or the motives of the patients; the other, the small number of papers published by judicial pathologists, each recording perhaps a single case which to the writer appeared to suggest that a definite relationship might exist between the tumor and the trauma. Even in these cases there remains only the post hoc propter hoc type of logic, and no matter how much one may respect the powers of accurate observation shown by these pathologists and the integrity of their statements, one is bound to note that most of their papers, also, arbitrarily assume the importance of the trauma as an observed external factor. Ribbert,<sup>24</sup> who thought that all the statistical collections were without value, stated that well studied single cases of this type might be more convincing than any heretofore published statistics.

The early literature is more confusing than helpful and contributes practically nothing to the subject. The dissertation of Siegfried Wolff,<sup>25</sup> which appeared in 1874, is often quoted because the author made an

20. Curtis, M. R.: Oral communication.

21. Schimmelbusch, quoted from Machol by Lubarsch-Ostertag: *Ergebn. d. allg. Path. u. path. Anat.* **1**:527, 1895.

22. Askanazy, quoted from Sauerbruch: *Deutsche Ztschr. f. Chir.* **100**:1, 1926.

23. Thiem: *Handbuch der Unfallkrankungen*, ed. 2, Stuttgart, 1909, p. 589.

24. Ribbert: *Zentralbl. f. Chir.* **25**:1195, 1895.

25. Wolff, Siegfried: *Zur Entstehung von Geschwülsten nach traumatischen Ernwirkungen*, Inaug. Diss., Berlin, 1874.

attempt to survey all the cases of tumor that had appeared in the University Surgical Clinic in the preceding ten years and to determine the frequency of trauma in these cases. The paper includes many cases which indicate a relationship between the tumors and chronic mechanical irritation due to foreign bodies, scars due to burns and lacerated wounds, but does not present any clinical evidence that is pertinent to the importance of the single acute trauma. Only one case, that of a carcinoma of the breast, is even worthy of mention; it will be cited in the following pages. Wolff enumerates, therefore, so few cases of single trauma followed by carcinoma, and these of such dubious certainty, that his conclusions should not be quoted in this connection.

On the subject of sarcoma caused by a single trauma, Wolff has been quoted as offering slightly more evidence, but in many of the cases that he cites, the injury was not at the exact point of the subsequent tumor and in many the tumor appeared only following a fracture or a contusion; of 100 cases of sarcoma of all types, 20 were found to have been preceded by traumas. A critical study of these cases was not made by Wolff.

The lengthy paper of Löwenthal,<sup>26</sup> appearing in 1895, contained a survey of 358 cases of tumors each preceded by an acute trauma, from among 800 observed at the Pathological Institute at Munich from 1870 to 1895. This paper has been widely quoted because of the large number of cases reviewed. So little critical survey of these cases has been made and the hospital histories have been employed so freely as evidence that little is contributed for the acute and no more is proved for the chronic types of traumatization.

Löwenstein,<sup>3</sup> in 1910, in a long monograph on the subject, analyzed 261 cases of malignant tumor compiled from the literature, 7 from the Samariterhaus at Heidelberg and 3 from Frankfurt, all probably traumatic, according to the histories. This paper is superior to others because an attempt was made to apply critical standards to the histories, and the author appreciated the need of sound methods of judging case records. Tables are presented giving clearly the lapse of time between the injury and the development of the tumor, and he included only cases in which the injury was described as at the exact site of the subsequent tumor. This marked a new type of study of the records on the subject and indicated the increased critical attitude then beginning to show itself.

This paper followed the publication by Thiem of an important contribution revealing a change toward precision of thought, for in 1909 Thiem<sup>23</sup> formulated a set of postulates which have since been of great value in clarifying the subject. Thiem pointed out that, in coming to a decision as to the importance of trauma, it must be remembered that

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26. Löwenthal, C.: *Arch. f. klin. Chir.* **49**:1, 1895 (bibl.).



trauma does influence the localization and course of other diseases, such as tuberculosis, osteomyelitis and pneumonia, although specific causative factors are well known for these diseases. Therefore, even "if several cancer parasites" should be discovered, the factor of trauma might still be important. Nevertheless, he wrote that "trauma is not the real cause of tumors" and that "among the accessory causes it plays a very important rôle."

Thiem's postulates were (1) that definite proof of the accident must be offered; (2) that the trauma must have been of sufficient severity to be effective; (3) that the tumor need not be at the exact site of the injury but must be definitely related to it, as is *contre-coup* laceration of the brain, and (4) that the interval between the accident and the appearance of the tumor must be a reasonable one; for sarcoma, this was stated by Thiem to be not under eight days, and for carcinoma, not under three or four weeks. At present, students of tumors would not accept these shorter intervals, because of the large amount of accurate knowledge which has been recently accumulated to show that a much longer time is required. In 1913, Graef<sup>27</sup> published a more complete monograph, contributing a collective review with a bibliography of 161 references. The author restricted his cases to those with only a single acute trauma. This paper includes also summaries of the more important monographs, and the general statistics are based on the cases as included in these various papers. Many of the cases he included, however, though following acute trauma, were preceded by old scars, irritation with foreign bodies and other irritants of various types, and therefore should not properly have been included. While the paper is useful and is written with considerable understanding, Graef without much discrimination allowed unimportant contributions to appear in it. This applies especially to many of the cases of carcinoma cited; those, for example, of the internal organs. Graef was, on the whole, skeptical as to the real relationship between trauma and tumor and advised great caution in assuming a direct relationship.

American literature contains three brief papers of real value, giving excellent reviews of the general situation. One is that by Ophüls,<sup>28</sup> published in 1921. Although brief, it is conservative and clearly formulates the absolutely essential conditions which must be complied with in awarding any verdict.

The second, by Mock and Ellis,<sup>29</sup> published in 1926, covers much the same ground and describes nine cases believed by them to fulfil

27. Graef, W.: *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* **17**:603, 1913 (bibl.).

28. Ophüls, W.: *California State J. Med.* **19**:54, 1921.

29. Mock and Ellis: *Trauma and Malignancy*, J. A. M. A. **86**:257 (Jan. 23) 1926.



many of the postulates that would place the cases in the group of neoplasms related to traumas and therefore entitle the patients to compensation, even though the tumors were not necessarily caused by the injuries. The authors pointed out the obligation of the surgeon to decide whether or not a particular case of malignant growth could be ascribed definitely to trauma, and they stated that there is no justification for deciding this in any particular case unless a relationship can be proved with scientific accuracy; and that cases as commonly reported offer no such scientific proof.

The third paper, also published in 1926, by Ewing,<sup>30</sup> calls attention to the requirements which he regarded as necessary to a sound verdict, and cites one carefully observed instance of a tumor arising after an injury and believed by him to be due to it. The paper is valuable, also, because of the concrete expression of opinion with regard to the rôle of trauma in definite types of tumors. His is a simple statement which, if followed, would rule out many of the cases now under discussion in the courts. The requirements laid down by Ewing are clear and closely in accord with those of Thiem, but are perhaps more definite, and in discussion of them the author especially warned against certain fallacies. These requirements are as follows:

1. The authenticity and the sufficient severity of the trauma must first be established.
2. The previous integrity of the wounded part must be shown. Löwenthal did not require this, and for that reason Ewing justly eliminated his paper from consideration as a valuable scientific contribution.
3. The identity of the injured area with the site of the subsequent neoplastic growth must be demonstrated.
4. The tumor must be shown to be a type which could result from trauma. Under this heading the author eliminated tumors due to congenital rests.
5. The proper interval of time must be proved to have elapsed.

For practical purposes these requirements, which have gradually been evolved from the experience of physicians and pathologists during the last fifteen years, are of the greatest importance. While they do not reach, and cannot reach, the theoretical truth, it is obvious that they are all that can be adhered to by any one forced to make a decision in a concrete case.

*Authenticity of the Trauma.*—The question of the authenticity and severity of the trauma is largely a legal one and is of no interest from

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30. Ewing, J.: *Am. J. Surg.* 40:30, 1926.

the medical point of view. It is well known that it is frequently impossible to establish authenticity by the accounts of eye witnesses, who are often far from observing the truth, and that the severity of a trauma has therefore to be judged by its objective results rather than by its aspect to the patient at the moment of its infliction or in retrospect. It is well known that the possibility of financial gain adds greatly to the importance of many traumas, in the minds of the patients, and that injuries are constantly suffered which are forgotten when the opportunity to gain from them does not present itself.

*Previous Integrity of the Wounded Part.*—It is also becoming evident that to demonstrate that the tumor process had not already begun before the time of the injury is often impossible. Before the frequent roentgenographic study of injured tissues, especially in the neighborhood of the bones, this was much more difficult than it is at present. Most of the reports in the literature, it must be remembered, described persons who when they presented themselves had swollen traumatic lesions. But the injured areas were not immediately subjected to x-ray studies in the clinics. Now such lesions are immediately examined with the x-ray, and the cause of the hemorrhage or exudate often then becomes apparent. Even in a phalanx a pre-existing lesion of the bone may be found indicating a long-standing disease process. In one instance in which a typist broke her finger while writing, a hitherto unrecognized cystic chondroma was promptly demonstrated in a roentgenogram. In the bones of the forearm or the leg, chondromas or giant cell tumors not infrequently have in this way been discovered, and in the thigh and upper arm a destructive sarcoma, such as occurs more frequently in this region, may be found to have caused the absorption of bone. Such a tumor is entirely unknown to the patient, who in perfect good faith may state that a jar or fall, as in a trolley car, was the cause of a fracture of the bone. Surgical intervention in this case discloses a small amount of highly vascular tumor which has originated in the shaft of the bone, although the greater proportion of the mass consists only of blood and could be easily mistaken for a hematoma even on microscopic examination. All injuries that are likely to be cited in claims for compensation should therefore be required to be subjected to study by the x-ray when the patient is first seen, if a trauma in or about the bone can possibly be implicated. The lengthy series of cases hitherto reported in the literature would be more useful and more interesting if such studies had been made.

*Identity of the Injured Area with the Site of the Neoplasm.*—It would seem evident that the trauma must bear some direct anatomic relation to the situation of the tumor. According to Ewing, the sites

must be identical. He assumed also that the well known results of transmitted injury, such as a tear in the meninges or the cortex from a blow on the jaw, are understood to be an essential part of the primary damage. Ewing, however, denied the possibility of causing a tumor of the internal organs by external injury, thereby ruling out all intra-abdominal growths and admitting as possible one neoplasm, only, of the chest, which was reported to be due to an injury of the skeletal tissues. In this instance, also, it might be assumed quite properly that pleural adhesions, with damage to the visceral pleura, followed the external trauma and that the case belongs therefore in the group due to chronic irritation.

There are included in the literature reports of trauma to one portion of the thigh or buttock, followed after a shorter or a longer period by sarcoma of the femur of pelvis. In such a case, a direct anatomic relationship cannot be established between the point at which the trauma was inflicted and that at which the tumor appeared. But, according to the laws of mechanics, the maximal injury is sometimes transmitted to a different point from that at which the injury is applied; as, for instance, in the case of a Colles fracture of the wrist. These principles have not always been taken into consideration in the published records. I have not found examples of bone or periosteal sarcoma reported as found in the hundreds of thousands of cases of calluses which must have resulted from the Colles fractures which are seen every year.

In this connection may be mentioned one of the only two cases which L. Pick<sup>31</sup> considered worthy of consideration. It was a fibrosarcoma of the humerus, which appeared as a swelling over the bone in May, 1927. The patient had sustained a compound fracture of the ulna in June, 1918, with resulting infection and sequestrums. The arm was healed in September, 1923, and the tumor did not appear until May, 1927. Here again there is confusion of thought as between a chronic and an acute trauma. The acute trauma preceded the appearance of the tumor in this case by nine years; and irritation was no doubt present over most of this period. Lubarsch,<sup>32</sup> however, expressed the belief that a hard fibrosarcoma might possibly follow an injury by three or four years.

*Required Lapse of Time.*—The interval of time which must elapse between the injury and the appearance of the tumor in order even to suggest a causal relationship, as reported in the literature, is extremely variable. Most of the figures in the literature, however, are drawn from patients' statements as to the correlation.

31. Pick, L.: Med. Klin. 17:416, 1921.

32. Lubarsch, quoted by Pick: Med. Klin. 17:416, 1921.

Ziegler<sup>33</sup> stated that the tumor must be visible as soon as the acute swelling of the trauma has subsided; and Ribbert believed that the time must be at least short, but did not arbitrarily specify any period. Bérard<sup>34</sup> and Thiem<sup>35</sup> more or less agreed that the time for the development of a sarcoma might be from eight days to one year, for carcinoma, from three weeks to three years and for glioma, from one month to ten years. Villata<sup>35</sup> stated that it must be from a few weeks to eleven years. Ewing<sup>36</sup> called attention to the fact that some tumors are of slower growth than others and pointed out that an advanced sclerosing osteogenic sarcoma of one of the long bones certainly requires "months" to be large enough for detection, and that inside this period such a tumor cannot possibly have been caused by the trauma. Virchow,<sup>1</sup> on the other hand, recognized the fact that bony metastases could develop rapidly, but did not specify any time, and Edward Miller<sup>36</sup> showed from x-ray plates and autopsy records that large nodules of round cell sarcoma developed in the lung in two and one-half weeks. Round cell sarcoma and lymphosarcoma are, however, known to be tumors of extremely rapid growth, as can often be observed in subcutaneous nodules. The writers who believed that glioma is related to trauma accepted a much longer interval of time between the trauma and the appearance of symptoms; Bérard stated that it might be ten years, and other writers considered that it might be even from thirty-five to forty years.

It is because of the uncertain duration of this interval that an attempt has been made to establish the importance of bridging symptoms which might seem to connect in some way the injury with the trauma, Ziegler having stated that unless the tumor appears immediately, there must be intermediate related symptoms. These are generally either intermittent or continuous pain, and are therefore very difficult to evaluate because there are seldom objective symptoms to add weight to the patient's statements.

Sometimes the interval between the trauma and the tumor has been assumed to be extremely short, even a few days, and therefore it might be well to recall that in a short-lived animal like the mouse, tar cancer rarely appears until three months have elapsed, and that in the rat sarcoma due to the injury inflicted by *Cysticercus* apparently requires at least eight months from the beginning of the irritation to the demonstration of

33. Ziegler, E.: München. med. Wehnschr. **42**:621 and 650, 1895.

34. Bérard, L.: Conference internationale pour l'étude du cancer, Paris, 1910. p. 355.

35. Villata, G.: Policlinico **32**:451, 1925; abstr., J. A. M. A. **85**:1338 (Oct. 24) 1925.

36. Miller, Edward: IX Congress der deutschen Roentgenesellschaft, 1913.



a tumor; and yet both these agencies are extremely effective carcinogenetically, giving rise to a high percentage of tumors in suitable strains. Such periods in these short-lived rodents are comparable with periods of from five to ten years in man. The same long period has been found to elapse in a case of chronic dermatitis due to irritation by the x-ray before the appearance of a neoplasm; yet this type of chronic irritation is also effective in the production of cancer. In the light of these facts it seems difficult to believe that a single injury inflicted a few weeks before, can act as an effective cause of a neoplasm.

#### BENIGN TUMORS

It is generally conceded that few benign tumors bear any relationship to acute trauma. In all the statistics devoted to this subject, they are regarded as less numerous than the malignant ones. It is of interest that Löwenthal and other writers, however, who found a high percentage of malignant tumors related to single traumas also found a higher percentage for the benign ones. For instance, Löwenthal, who believed that 84 per cent of the malignant tumors were caused by traumas, also claimed that 16 per cent of the benign tumors had this etiology. On the other hand, Würz,<sup>37</sup> among 129 benign tumors, found only 3 per cent in which there appeared to be the slightest relationship to single traumas. Bérard<sup>34</sup> pointed out that many benign growths were classed as tumors in the literature, which actually were only inflammatory lesions, which are known to be sometimes related to traumas. But he included here, as inflammatory, the lipomas, the fibrolipomas and the myxolipomas and the osteomas of the cranium, forearms and adductors, a classification which would by no means be adhered to by most writers. It is also a matter of terminology whether an organized hematoma is sometimes classed as an angioma, or whether its inflammatory nature is recognized at the time it is examined. The epithelial cysts, which are generally admitted to be traumatic, were shown by Hesse<sup>38</sup> to be due frequently to epithelization of hair follicles and other derivatives of epithelium.

*Lipoma.*—Würz<sup>37</sup> carefully analyzed the histories of twenty-eight patients with lipoma and concluded that only one of the tumors could be suspected of being a traumatic one. The patient, a woman, had sustained a fall in which the left side of the pelvis was seriously contused and she had suffered continuous pain in the buttock for a few weeks; then, on examination, a large lipoma, apparently actively growing, was found embedded in the fat. This tumor might be placed in

37. Würz, K.: Beitr. z. klin. Chir. **26**:567, 1900.

38. Hesse, F. A.: Beitr. z. klin. Chir. **80**:494, 1912.



the group of fat necroses described by Lee and Adair<sup>39</sup> and may have been only an instance of active regeneration and not of neoplastic growth; or a preexisting tumor may have been rendered painful by the contusion.

Siegfried Wolff<sup>25</sup> believed four of his cases of lipoma to be traumatic. One of them followed a single injury. The others appeared on the shoulders following repeated contusions. Since this is so common a situation for lipoma, even in those whose occupations do not cause them to sustain injuries to the shoulders, its relationship to this trauma seems to be largely imaginary.

Stern<sup>40</sup> studied this type of tumor and decided that it could not be in any way connected with an injury. Bosse and Lieschke<sup>41</sup> believed that they had watched the origin of several cases of scrotal lipoma secondary to contusion, and Lieschke<sup>42</sup> collected sixty-two cases in which he believed that there was possibly a traumatic origin. These tumors, also, were described before the frequency and nature of traumatic fat necrosis and regeneration were well understood.

*Myxoma and Angioma.*—Evidence has not been reported that a case of myxoma or of true angioma has ever been caused by a trauma.

*Myoma.*—Myoma of the uterus is also not caused by trauma, direct or indirect. The question has been raised because of the astounding case described by Schneider<sup>43</sup> of a woman who, struck by a calf in the right lower abdominal quadrant, suffered a hemorrhage and a miscarriage. Abortion occurred in two succeeding pregnancies, and after four and a half years she was found to have a fibroid uterus. Leopold believed that the wide occurrence of fibroids among all types of women rendered it impossible to associate them with special traumas.

*Fibroma.*—Cases of fibroma were studied also by Wurz,<sup>37</sup> who believed that none was referable to trauma. Graef<sup>27</sup> thought some of them might be, and Audain<sup>44</sup> referred to the traumatic fibromas and sarcomas in the Haytian negroes as malignant tumors, but these are now known to be keloids.

Sontag and Tendeloo,<sup>45</sup> quoted by Sauerbruch,<sup>46</sup> believed that the fibromas were usually traumatic, but the prevailing view at the present

39. Lee and Adair: *Ann. Surg.* **72**:188, 1920.

40. Stern: *Ueber traumatische Entstehung innern Krankheiten*, Jena, 1913, p. 487.

41. Bosse and Lieschke: *Therap. Rundschau* **3**:433, 1909.

42. Lieschke: *Lipom und Trauma*, diss., Berlin, 1911; quoted by Graef (footnote 27).

43. Schneider: *Unfall und Gynecologischen Erkrankungen insbesondere Myome*, diss., Munich, 1912.

44. Audain, quoted by Graef (footnote 27).

45. Sontag and Tendeloo, quoted by Sauerbruch (footnote 46).

46. Sauerbruch, F.: *Deutsche Ztschr. f. Chir.* **199**:1, 1926.

is that of von Hansemann,<sup>5</sup> who considered all these tumors in which there is a traumatic history, as inflammatory and due possibly to foreign bodies or infections. Many of the tumors of the anterior abdominal wall classed as desmoids are generally considered to be due to stretching lacerations or repeated contusions of the rectal muscles.

*Chondroma.*—The chondromas were believed by Lubarsch not to be caused by traumas, but to be stimulated to more rapid growth by them in some cases, especially if the injury was inflicted near to the epiphyseal line of one of the long bones. Graef<sup>27</sup> thought that a few of these tumors followed fractures of the ribs and were derived from cartilage, which is usually found in a normal callus, but that the chondromas of the organs were teratoid only. Roger Williams<sup>47</sup> admitted the possibility of an osteochondroma arising in this way from the cartilage cells in the callus following fracture.

*Adenoma.*—The adenomas cannot well be believed to have any relation to traumas. The inflammatory hypertrophies resembling adenomas are known to be frequent.

*Osteoma.*—The exostoses and osteomas are a somewhat intermediate group, the former being classed by Wood<sup>48</sup> among the inflammatory lesions. Many of the so-called traumatic osteomas are frankly chronic inflammations in origin (rider's bone) while others are now understood to be benign bony tumors which have existed for a long time and have finally been separated from the shaft of the bone by traumas. A blow or fall not infrequently separates an exostosis from the lower third of the humerus or femur and in this way brings the tumor to the notice of the patient. Such a tumor is found to have a concave inner surface and to have been detached by the violence along this line of cleavage. Würz,<sup>37</sup> however, thought that 40 per cent of these lesions were probably traumatic and believed that it was almost the only tumor that could be so considered. Graef<sup>27</sup> admitted that a certain proportion were traumatic, but pointed out the inflammatory nature of many of the tumors so classified.

*Osteitis Fibrosa.*—As osteitis fibrosa occasionally precedes giant cell tumor of the bone and is generally believed to be due to local, small, repeated hemorrhages, some writers—for example Sauerbruch<sup>46</sup>—believed that trauma may be one of the factors causing such hemorrhages and therefore ultimately a giant cell tumor, but that it is not the only cause. However, experimentally produced hemorrhages have

47. Williams, Roger: *The Natural History of Cancer*, New York, William Wood & Company, 1908.

48. Wood, F. C., quoted from Delafield and Prudden: *Text Book of Pathology*, New York, William Wood & Company, 1927, p. 1097.

failed to cause tumors. Looser <sup>49</sup> showed a case in which nearly every bone in the body contained the lesions of osteitis fibrosa, and pointed out that in none of these was there any history of trauma.

*Giant Cell Tumor.*—Ewing <sup>50</sup> believed that osteitis fibrosa may precede the hemorrhages which eventually produce giant cell tumor, but thought that there is not in such cases any traumatic history of importance. In several cases of supposed traumatic origin x-rays revealed disease of long standing. Sauerbruch <sup>46</sup> cited one case in which the patient sustained a blow on the forearm and in three months presented at the site a large giant cell tumor. Such records, are, however, infrequent. Some writers regarded the causative agent of the giant cell tumor as an infectious one.

#### MALIGNANT TUMORS

*Carcinoma—Superficial Types.*—Among the malignant tumors, the squamous type of carcinoma has been only rarely ascribed to a single trauma. In each case the diagnosis invariably depended only on the statement of the patient that the part was previously normal. For instance, the case reported by Hahn, <sup>50</sup> and quoted by Machol, <sup>51</sup> was that of a patient with a lacerated wound in the scalp for which he was treated in the hospital seven weeks; he returned seven months later because of an epithelioma in the same region. Another instance described is that of a patient who was observed to have an epithelioma of the tongue following an accidental bite. However, it has been pointed out by others that epileptic patients who bite their tongues continuously have never been found to have an increased frequency of epithelioma of that organ.

When carefully analyzed, nearly all the cases indicate that the original trauma resulted in a scar which was present for some time before the tumor appeared, or else that an effort was not made to ascertain that the tissues were normal before the time of the injury. This applies to the case of Dietrich, <sup>52</sup> in which an old scar was traumatized and some three months later an epithelioma appeared. The word of the patient was accepted that a neoplasm was not present at the time of the injury. Dietrich also concluded that the traumatism caused by a biopsy resulted in a great local increase in the rate of growth of the part of the tumor incised, but the pictures submitted in evidence scarcely bear out his conclusions.

49. Looser: *Deutsche Ztschr. f. Chir.* **189**:113, 1924.

50. Hahn, Otto: *Beitr. z. klin. Chir.* **26**:591, 1900.

51. Machol: *Die Entstehung von Geschwülsten im Anschluss an Verletzungen*, Strassburg, 1900.

52. Dietrich: *Neue Deutsche Chirurgie*, Stuttgart **35**:184, 1926.

Ewing<sup>30</sup> was uncertain as to whether it is ever justifiable to ascribe an epithelioma to an injury, and in any case he would not accept any causal relationship after one year. There are cases described as following a blow, a bite, a gunshot wound or a laceration even seventy-six years before, as mentioned by Melchior,<sup>53</sup> but in any case the two events can scarcely be shown to be related.

*Carcinoma of the Breast.*—Carcinoma of the breast is one of the types of carcinoma most frequently ascribed to injury, largely because the gland is superficial and subject to injuries, and because the tumors are difficult to palpate and generally painless until some special trauma causes structural changes due to hemorrhage. To ascribe the origin of a carcinoma to a single blow is as inaccurate and unscientific as it would be to judge of the duration of a tumor of the breast from the patient's statement, and any one who listens carefully to the statements of patients knows that carcinomas of the breast are generally stated to have been present for from five years to two days without regard in any instance to the size, position or type of the tumor. Compilations in the literature by Dietrich,<sup>54</sup> Frangenheim,<sup>55</sup> Schulthess,<sup>56</sup> Winiwarter,<sup>57</sup> Oldekop<sup>58</sup> and Ziegler<sup>53</sup> contain statements indicating that trauma preceded the tumor in from 1 to 25 per cent of the cases. This wide range of figures indicates only the impossibility of drawing accurate conclusions from the statements at hand.

Würz<sup>37</sup> stated that of 163 cases probably none was traumatic, and that in only 5 per cent can it even be suggested that a trauma was responsible for the tumor.

Graef<sup>27</sup> thought that Löwenthal's<sup>26</sup> twelve cases in the male breast should be discarded, as the rapidity of the growth of carcinomas of the breast in the male is well known. The three descriptions of cases by Machol<sup>51</sup> are entirely uncritical, as is most of his paper; some of the tumors that he cited developed a year after minor injuries, and one of them was never diagnosed microscopically.

Ewing<sup>30</sup> stated that a carcinoma of the breast can be assumed to have followed an injury only if the breast can be shown to have been previously normal and the injury to have been severe enough to have caused interstitial hemorrhage and solution of continuity of the breast ducts; also that there must be some indication of continuity of symp-

53. Melchior: München. med. Wchnschr. **63**:371, 1916.

54. Dietrich: Die Erkrankungen der Brustdrüse, Neue Deutsche Chirurgie, Stuttgart **35**:184, 1926.

55. Frangenheim, P.: Zweifel-Payr, Klinik der bösartigen Geschwülste, Leipzig, 1925, vol. 2, p. 663.

56. Schulthess, H.: Beitr. z. klin. Chir. **4**:445, 1889.

57. Winiwarter: Beitrag zur Statistik der Carcinom, Stuttgart, 1878.

58. Oldekop, J.: Arch. f. klin. Chir. **34**:536, 1879.



toms between the trauma and the appearance of the tumor and that even in these cases one can only maintain a probable relationship. He believed that the masses due to fat necrosis and regeneration resemble cancer, but stated that such a lesion is never followed by cancer.

*Tumors of the Internal Organs.*—It is almost universally agreed that tumors of the internal organs are not caused by single external injuries, but by chronic inflammatory processes and long continued traumatization. Ewing<sup>59</sup> stated that in the internal organs cancers can result only from long continued irritation, that gastric, rectal, pancreatic, hepatic and uterine tumors are so caused, and that neither these nor tumors of the lung, esophagus and gallbladder can be ascribed to acute traumas. Boas,<sup>60</sup> who collected a series of sixty-two cases of gastro-intestinal carcinoma which were alleged to be related to trauma, found that usually the asserted relationship was not possible; for example, a carcinoma of the pancreas had been alleged to be due to a fall on the back, and a carcinoma of the pylorus, to a fall on the sacrum. As such claims were manifestly absurd, he admitted only nine cases in which he thought even the slightest relationship might be indicated. Gockel,<sup>61</sup> in a lengthy article, described the chronic irritants which he believed were the only important agents in the production of tumor in these situations. Graef<sup>27</sup> believed that there was little, if any, relationship and that carcinoma of the stomach could never be caused by a trauma unless the trauma were severe enough to cause an ulcer in which the tumor finally developed. Menne<sup>61</sup> collected from the literature cases of this type in which compensation was awarded and cases in which it was refused.

*Lymphosarcoma.*—Pistocchi<sup>62</sup> recently described a lymphosarcoma of the stomach appearing five months after a severe contusion of the epigastrium with intense pain in the interim. The same degree of trauma, however, is frequently sustained by laborers and especially by prizefighters, without any known injury to the stomach. Lymphosarcoma of the stomach, in fact, is one of the rarest of the tumors. Furthermore, no one asserts that the commonly occurring lymphosarcoma of the cervical nodes is of traumatic origin.

*Hypernephroma.*—Hypernephroma of the kidney and the suprarenal gland is believed by most pathologists to be due always to a congenital rest; its occurrence does not bear any relationship to trauma. Rückart,<sup>63</sup> in a compilation of 117 cases in the literature, found trauma

59. Boas: Deutsche med. Wchnschr. **23**:707, 1897.

60. Gockel: Arch. f. Verdauungskr. **2**:461, 1896.

61. Menne, Ed.: Deutsche Ztschr. f. Chir. **81**:374, 1906.

62. Pistocchi, G.: Policlinico **30**:83, 1923.

63. Rückart: Deutsche med. Wchnschr. **49**:384, 1923.



mentioned only nine times, and himself thought that in each case the trauma had called attention to the tumor rather than caused it. Ribbert,<sup>64</sup> also, believed that the Grawitz type of tumor arises only from congenitally misplaced cells.

Sauerbruch,<sup>65</sup> on the other hand, observed a patient who had sustained a blow in the lumbar region severe enough to keep him in bed for three weeks, and who later appeared with an inoperable tumor in the region of the kidneys. The fact that he observed hemorrhage in the region of the tumor at autopsy cannot be adduced as evidence, since nearly all suprarenal tumors of any large size are hemorrhagic, even those in patients who have been in bed for months. Frangenheim,<sup>66</sup> however, considered the possibility of stimulating a quiescent suprarenal tumor of the cortex to active growth by traumatization.

*Pulmonary Tumor.*—A serious effort has never been made to ascribe pulmonary tumor to an injury. The case reported by Lepine<sup>65</sup> was that of a man who had sustained an injury to the chest wall and who one year later developed a squamous carcinoma of the lung beneath the site of the old injury. But serious injuries to the chest are so frequent and pulmonary tumors so rare that, statistically, a causal relationship is not even suggested.

*Choroidal Sarcoma.*—Sarcoma of the choroid has sometimes been claimed to be due to trauma, chiefly on the ground of its being vascular and hemorrhagic. Sattler<sup>66</sup> pointed out that it is not traumatic and he did not admit even that it can follow the chronic inflammations of the eyeball.

Wintersteiner<sup>67</sup> studied ninety cases of sarcoma each reported to have been caused by trauma but could find only four in which there seemed to be any possibility of it.

*Testicular Tumor.*—The tumors of the testicle, which are frequently classified in the literature as sarcomas, but which are more often either embryonal or mature carcinomas, have long been believed by some writers to be caused by trauma. Of the two types of testicular carcinoma, one arises from embryonal remnants present long before adult life, and the other, the adult carcinoma, or seminoma, arises from the germinal epithelium. Only with regard to the latter should there be any question of traumatic origin. Both types—the embryonal and the mature—grow rapidly, so that a blow one year before may not in any case be considered a cause. As has just been said, all the tumors

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64. Ribbert: Deutsche med. Wchnschr. **21**:9, 1895.

65. Lepine: Lyon méd. **100**:18, 1903.

66. Sattler, H.: Die bösartigen Geschwülste des Auges, Leipzig, 1926.

67. Wintersteiner, quoted in Lubarsch-Ostertag: Ergebn. der allg. Path., u. path. Anat. Ergänzungsband **10**:1044, 1907.

which can be shown to be teratoid should be excluded from the traumatic group. Some surgeons do not take this position, however; for instance, Coley,<sup>68</sup> who believed that a large percentage of the complex teratoid tumors were traumatic.

Virchow believed that tumors arose in the undescended testis more frequently than in the normal one, and ascribed the difference to chronic irritation. This greater frequency was affirmed by some, and denied by other recent writers (Bulkley<sup>69</sup>), who did not consider trauma as of any importance but believed it either caused hemorrhage in an already existing tumor and hence called attention to the growth or stimulated a tumor to increased activity. Many other writers have followed Siegfried Wolff,<sup>70</sup> who thought that as traumatic tumors they were second in frequency only to the bone tumors.

Brunne<sup>70</sup> collected thirty-five cases, in thirty-four of which there was record of injury to the testis, but described only one in which evidence existed that a normal gland had been present prior to the injury.

Weinert<sup>71</sup> reported a case of a trauma of the right testicle followed by an increase in size of the gland. Extensive metastases quickly caused the death of the patient. The tumor was a large cell sarcoma (seminoma), and Weinert thought that a causal relationship could not be traced between the trauma and the neoplasm.

*Sarcoma.*—The most important and perplexing portion of the discussion has centered around the question of the relation of cases of sarcoma of the bone and of fascial sarcoma to trauma. All the groups were included in the long reviews mentioned, but the percentage of cases thought to be due to trauma will not be given here because of the obvious discrepancies in the observations of different writers and the fact that their work has not been subjected to critical analysis. Ribbert<sup>24</sup> stated that occasionally single cases were difficult to explain; but he willingly denied any general relationship. A case described by Ott<sup>72</sup> is of interest. A boy, 2½ years of age, was bitten by a dog on the forearm. The lesion continued unhealed for four weeks. The scar became much thickened in three months, after which an ulcer was excised. This was said to be a small round cell sarcoma; but no type of malignant tumor is more readily confounded with chronic inflammation, for example, syphilis. How difficult it may be to make such a

68. Coley, W. B.: *Ann. Surg.* **76**:370, 1923.

69. Bulkley: *Surg. Gynec. Obst.* **17**:703, 1913.

70. Brunne: *Ein Fall von Hodensarkom auf traumatische Basis*, Diss., Greifswald, 1903.

71. Weinert: *Handbuch der aerztlichen Erfahrungen im Weltkriege*, Leipzig, 1921, p. 51.

72. Ott: *München. med. Wchnschr.* **57**:103, 1901.

morphologic differentiation, is illustrated by an amputation done at the instance of a well trained pathologist who could not differentiate on a biopsy between round cell sarcoma and syphilis. Clinically the condition resembled sarcoma. Many descriptions of allegedly traumatic cases, unaccompanied by a microscopic section, an x-ray photograph or a statement of the clinical outcome, fall into the anecdotal group; they cannot be accepted as having as much probability as some of the cases of bone sarcoma, which are more completely described and the microscopic diagnosis of which cannot be challenged. Graef<sup>77</sup> believed that sarcoma more frequently followed the crushing injuries, both moderate and severe, but not open wounds. Ewing<sup>80</sup> asserted that neurogenic sarcoma is never traumatic in origin, but has a congenital basis. The osteogenic spindle cell type of tumor he regarded differently; he described such a growth which arose over the patella after a fall on the knee, and caused complete disability and constant symptoms until death six months later. In so important a tendon as that of the quadriceps, the question of a preexisting tumor being responsible for the fall cannot be excluded on the basis of the case report.

The three lengthy articles by Coley<sup>73</sup> on bone sarcoma and other types of malignant tumor, in which he stated that of 270 cases of sarcoma personally observed, 60, or 31 per cent, and of 800 subsequent cases, including 61 different types of cancer, 179, or 23 per cent of the whole group were associated with trauma, do not, after careful reading, in my opinion, justify the conclusion that the trauma was associated in a causal relationship. That the trauma was antecedent is all that can be concluded. Coley discussed a large group of these cases, which he said must properly be called cases of "acute traumatic malignancy," but the meaning of such a term, although used at one time especially by the English, is somewhat ambiguous, and the tumors, which appeared within a week, cannot be understood to have been caused by trauma. The conclusions in the three papers are essentially the same.

Mock and Ellis,<sup>79</sup> as well as others, thought that "not more than half of these cases were even fairly convincing." Coley himself selected six which he thought could not fail to convince the most skeptical, and these are, in fact, the only ones which are not open to serious doubt.

Kolodny<sup>74</sup> pointed out that the trend of modern thought with regard to bone sarcomas, as with other types of malignancy, is to look for many causes, not one only. He agreed that trauma was "frequently

73. Coley, W. B.: *Ann. Surg.* **27**:259, 1898; *ibid.* **53**:449 and 615, 1911; *M. News* **78**:575, 1901.

74. Kolodny: *Bone Sarcoma, Surg. Gynec. Obst. (suppl. 1)* **44**:5, 1927.

associated with the origin of bone sarcoma" and pointed out the similarity of some bone tumors to callus formation in vascularity, cell morphology and clinical appearances. Although conceding these points, he gave the reverse side of the discussion full weight; that is, the rarity with which a trauma produces a tumor suggests that the single trauma is not even an adjuvant etiologic factor, and that there is a more profound predisposing factor in the persons who have tumors.

The case described by Amberger<sup>75</sup> is not difficult to understand; it illustrates, however, a type of tumor which, because of its obscure position, is often regarded as having an obscure cause. His patient, a young man of 19, in good health, had sustained a fall on one of his buttocks on the ice. This was followed by severe pain in the buttock. An accompanying injury of his scalp kept him in the hospital for three weeks. X-ray photographs of the painful buttock taken at the time did not show lesions. Three weeks afterward, the pain involved the sciatic nerve, and six weeks after the injury, a swelling in the buttock could be noted. A microscopic examination of the tumor was not made. At the end of the next three months, the patient died with an enormous tumor and generalized metastases.

Many cases of tumor of the pelvic bones similar to this one have taken much longer than this did to appear on the surface. Furthermore, the x-ray photographs often have not revealed abnormal conditions, despite the presence of a growth for a much longer period than that covered by the x-ray examinations. It is too often forgotten that an extensive neoplastic growth may surround a bone and give no demonstrable shadow until bone absorption begins. This solution of the bone substance may be delayed for a long time. The tumor in Amberger's case eventually involved the iliac bone but could not under any circumstances have been detected by palpation or x-ray in the beginning. It seems much more probable that the muscular control necessary in skating was disturbed by the presence of the tumor and that this caused the original fall through a loss of balance. Had the patient not fallen, the tumor might not have come to his observation until a few weeks or months later. The fall added to the disability of the patient, but it did not by any means offer proof that it had caused the tumor.

Haberern,<sup>76</sup> in 1892, collected and discussed cases of the so-called callus sarcoma, when reporting his own case; he quoted Bruns to the effect that the descriptions of the sixteen cases in the literature were lacking in both anatomic and microscopic details. Haberern's case was that of a man of 54, who fell under a heavy wagon, which passed

75. Amberger: *Monatschr. f. Unfallh.* **17**:69, 1910.

76. Haberern: *Arch. f. klin. Chir.* **43**:352, 1892.



across his chest and the left humerus, causing a comminuted fracture of the latter above the condyles. This was put in a splint for six weeks. It was then regarded as normally healed and was treated with baking and massage. The patient was not seen again for nine months. At the end of this time he returned with a large, painful osteochondrosarcoma at the site of the old fracture. This had been growing for two months. This case appears to have been carefully scrutinized, with the exception that roentgenographic studies were not made. It is of more interest than most of the published examples, because of the history of violence applied directly at the site, the period of observation after the fracture and the microscopic examination in which the growth was clearly described as malignant.

Of these cases of various types of sarcoma the last case illustrates the real problem; for in it one sees that, though the clinical records seem convincing, there must always remain the possible explanation of a small, unrecognized, previously existing tumor, in view of the enormous number of fractures occurring annually, following which neoplasms do not arise.

*Tumors of the Brain.*—Even writers who did not admit the traumatic origin of bone tumors, were inclined to acknowledge a probability that some of the cases of glioma reported were related to cerebral injuries; von Hanseemann,<sup>5</sup> Dürck<sup>77</sup> and Reinhardt<sup>78</sup> were among the number. It must be accepted, however, that glioma offers the greatest difficulty because it is even more completely concealed from observation, and in the cases detailed in the literature the injuries described by the patients occurred at a much earlier period than the traumas in the other types of neoplasm alleged to be due to trauma. There are great variations in the statistics on this subject. The long compilation by Adler,<sup>79</sup> consisting of 1,086 cases, from which he derived the conviction that 88 per cent were related to trauma, presents many difficulties to a critical reader, as the injuries described do not appear to show any important connections between the trauma and the tumor; also distinction is not made between types of cerebral tumors.

Modern methods of histologic technic have shown that the gliomas form a complex group and that there is always danger of confusing certain types of proliferative gliosis with true neoplasms.

Gerhardt,<sup>80</sup> in a series of sixty cases, ascribed 17 per cent to traumas, and Monakow,<sup>81</sup> in a series of forty-one cases, believed that 24 per cent

77. Dürck, H.: *Klin. Wchnschr.* **3**:658, 1924.

78. Reinhardt, G.: *München. med. Wchnschr.* **75**:399, 1928.

79. Adler: *Arch. f. Unfall.* **2**:189, 1897.

80. Gerhardt: *Das Gliom, Würzburger Festschrift*, 1882, vol. 2.

81. Monakow: *Schweiz. Arch. f. Neurol. u. Psychiat.* **14**:289, 1924.



were traumatic. Hübschmann<sup>82</sup> believed that in a series of 107 cases, 75 per cent were probably, though not certainly, traumatic. Reinhardt,<sup>78</sup> on the basis of war injuries, said that tumors of the brain had not increased and that therefore the inference of a traumatic cause for them was to be denied. Neubürger,<sup>83</sup> however, described two cases of glioma each of which followed six years after a cerebral injury sustained in the war. Nevertheless, he was unable to show that the gliomas had not arisen on a basis of chronic irritation of the supporting substance of the brain, as extensive chronic connective lesions were also present. He acknowledged that a special cellular disposition of the brain of the patient must have been concurrently present, as most cerebral injuries of the same type do not give rise to gliomas.

Reinhardt<sup>78</sup> believed that in order to establish that a tumor of the brain or the meninges was caused by a trauma it must be shown that the tissues had been lacerated, that between the trauma and the first symptoms of the tumor there had been at least several weeks without symptoms and that the tumor is at the point of injury; further, the morphology and histogenesis of the tumor must be definitely stated.

An interesting case was described by Reinhardt, in which a gliosarcoma occupied a portion of a frontal lobe in a patient who had sustained an injury due to a foreign body, which apparently had entered the orbit and embedded itself in the frontal lobe twenty years before. The foreign body was a metallic fragment, 1 cm. by 0.33 cm., and it was removed from the tumor at autopsy. The gliosarcoma can scarcely be alleged to have arisen from a single trauma, but rather from a chronic irritation.

The frequently quoted cases described by Becker,<sup>84</sup> who questioned many of the uncritical statistics in the literature, added only another to the improperly included cases. The recorded history should be accepted only as an example of the utterly unscientific and untruthful accounts which obscure the literature. The patient, a coachman for the physician who observed the case, suffered a severe contusion of the head from an accident in which his horses were suddenly startled and he was thrown to the ground. Afterward deafness slowly developed in the left ear, so that the physician was obliged to shift his position to the right side of his driver. Nausea, vertigo and altered personality followed in due course. The man died. A gliosarcoma was disclosed at autopsy. The astonishing observation was made by the physician that although the patient had been suffering from frequent headaches prior to the blow on the head, he did not think that the tumor of the brain had been already established, since the man had been able to pursue his regular work.

82. Hübschmann: *Deutsche Ztschr. f. Nervenhe.* **66**:1, 1920.

83. Neubürger, K.: *München. med. Wchnschr.* **72**:508, 1925.

84. Becker: *Aerzt. Sachverst.-Ztg.* **16**:153, 1910.

The single case reported by Richter,<sup>85</sup> in which an endothelioma of the dura developed on the inside of the skull of a man who thirty-eight years before had been injured by the fall of an iron kitchen utensil and rendered unconscious for fourteen days, is highly circumstantial.

Ewing did not accept the traumatic origin of endothelioma nor did he believe that glial cells regenerate easily. He stated that most of the tumors of the nervous system are referable to disturbances in the structural development of the ectoderm.

Von Hanseman<sup>86</sup> thought that gliomas are altogether too few when compared with the large number of injuries of the head to make their occurrence of any importance as a causative agent. He also stated that a latent tumor may suddenly give symptoms if an unusual movement such as bending or straining causes the spaces and vessels of the tumor to become engorged.

It is therefore the tendency of the more recent writers to question seriously a traumatic origin for glioma as for the other types of tumor and to feel that logically there is no reason to connect whatever injuries may have been sustained by the head years before with the presence of a primary tumor of the brain.

#### EFFECTS OF TRAUMA ON A PREEXISTENT TUMOR

The general subject of what may be expected to be the effect of a trauma on a preexisting tumor is important, as, unquestionably, positive results will be presupposed in every case by the lay mind, and many of these cannot be scientifically excluded. Lubarsch believed that changes in a preexisting tumor could be attributed to a tumor only if the injury was such as to cause a change in the metabolism of the cells, and such as to increase the rate of growth of the cells; and if histologic investigation of the trauma showed the results of hemorrhage, that is, phagocytosed blood pigment and altered vessels. Lubarsch, however, recognized the fact that untraumatized tumors do not grow with any regularity and that considerable periods of rest may alternate with active periods of growth, a phenomenon which has been abundantly studied in the tumors of animals (Woglom<sup>86</sup>). This is a factor dependent to a considerable extent on the biology of the individual tumor; for certain tumors, such as vascular hypernephromas, apparently enlarge rapidly for a time, but spontaneous hemorrhages are frequent, and following these, regressions—probably due to thrombosis and hemorrhage—are frequent. Other tumors of the more fixed, scirrhus type, such as many of the carcinomas of the breast and the adenocarcinomas of the sigmoid, are

85. Richter, H.: *Klin. Wchnschr.* 5:1617, 1926.

86. Woglom, W. H.: *The Study of Experimental Cancer*, New York, Columbia University Press, 1913.

relatively avascular, and do not fluctuate in size. It is difficult to produce hemorrhage in them even by direct traumatization; they are scarcely ever found to be hemorrhagic at operation, except when massage or manipulation has been carried out immediately before, and even then only the superficial portions of the tumor are ever seen to be affected and they but slightly. It cannot be denied that a tumor, for instance of the recto-sigmoid junction, already adherent to the sacrum might be slightly detached from the bone, or that sufficient traumatization might occur over the periosteum through a direct blow or a hard fall to cause increased pain in the tumor. There is also the possibility that a pedunculated tumor might become acutely painful following a fall or a blow because of torsion of a peduncle with attendant hemorrhagic infarction, and thus attract the patient's attention. A pedunculated myoma of the small intestine of an extremely vascular type has been known to perforate through the serous covering at the moment when the patient lay down for examination and before any pressure had been exerted on the abdomen. Should this occur coincidently with any external violence, the perforation would be attributed by the patient to the trauma. Unquestionably, sufficient traumatization might hasten such a perforation.

A trauma may, also, by depressing the vitality of the tissues, favor the localization of infection in a tumor, and lead to subsequent suppuration. Necrosis and even gangrene might occur as a result of a sufficiently severe trauma applied to certain portions of a tumor if it involved a peduncle or the major portion of the blood supply. Infection may frequently cause regression in the size of a tumor by giving rise to numerous thromboses, and this is especially true in the case of lymphangiomas and other tumors which may become infected with the streptococci. The streptococcus of erysipelas is especially likely to cause thrombosis of thin-walled capillaries. Von Hansemann believed that trauma might accelerate growth. That this is not a necessary result of the trauma, however, was shown by Rohdenburg,<sup>87</sup> who collected instances of the partial removal of tumors which did not show accelerated growth resulting, and which did show disappearance for a long period. The experiments carried out by Wood,<sup>88</sup> in which biopsies were performed on carcinomas transplanted in mice, failed to show acceleration of the rate of growth of the tumors following the incisions.

Stern<sup>40</sup> stated that no doubt many tumors grow faster as a result of traumas, but that there cannot be a general rule for this; that perforation of a preexisting carcinoma of the stomach is possible, but that this also cannot be proved to be due to the trauma. There does not seem

87. Rohdenburg, G. L.: *J. Cancer Research* 3:193, 1918.

88. Wood, F. C.: *Diagnostic Incision of Tumors*, *J. A. M. A.* 73:764 (Sept. 6) 1919.

to be any doubt that sarcomas of the extremities are frequently aggravated, symptomatically at least, by superficial injuries. Periosteal lesions are notably painful ones, and a blow severe enough to cause hemorrhage in the periosteal covering of a tumor or in the superficial parts of a tumor derived from the periosteal layers of the bone no doubt aggravates the symptoms endured by the patient and fixes his attention on the lesion. It is quite possible that a moderate traumatization of the skull might cause an extensive hemorrhage in a tumor of the brain and thus reveal a hitherto unsuspected neoplasm. It is conceivable, also, that the cellular portion of such a growth might be in some cases temporarily stimulated by the congestion or vascularity resulting from hemorrhage and by the subsequent repairing which may be the consequence of the trauma; but the opposite possibility must be kept in mind, which is that necrosis of a portion of the tumor and subsequent shrinkage may also be directly due to the injury.

The gastro-intestinal tract can sustain lacerated wounds as the result of external injury, especially the anterior coils of the small intestine (Vance<sup>89</sup>). More rarely one of the other portions of the intestine or of the colon may be ruptured. The duodenum or the colon may be contused severely enough to cause tears, thrombosis and necrosis. If a preexisting tumor of the gastro-intestinal tract is injured in this way, it is conceivable that the tumor cells might be more widely distributed than would otherwise occur. This is true also in the case of a rupture of ovarian or other cysts which contain viable cells, which may become readily implanted on remote peritoneal surfaces. The fixation of the tumor is a most important factor. Organs such as the esophagus, which are entirely inaccessible to outside influence, do not rupture from external violence. Numerous decisions against compensation in cases of carcinoma of the stomach and esophagus were cited by Engel.<sup>2</sup>

Sebestyén,<sup>90</sup> in a recent compilation of 4,068 cases of sarcoma, found that 15 per cent belong to the group of so-called traumatic sarcomas of the bone. He included three of his own cases in which the traumatic influence seemed to him unusually probable. The first was that of an infantryman, aged 23, wounded in the right shoulder in 1916 by a blow from a gun stock. The joint remained painful and swollen with limited motion for two months. There was a venous dilatation over the area, but not any scars. The x-ray showed a thickening of the cortex and a radiating bony deposit extending into the soft parts. Evidence of fracture was not seen. Diagnostic incision showed a spindle cell sarcoma

89. Vance, B. M.: Subcutaneous Injuries of Abdominal Viscera: Anatomic and Clinical Characteristics, *Arch. Surg.* **16**:631 (March) 1928.

90. Sebestyén, J.: *Arch. f. klin. Chir.* **136**:716, 1925.



with osteoid deposits. The patient died two weeks later. An autopsy showed general sarcomatosis with widespread metastases.

The second case was also that of an infantryman, aged 26, wounded in March, 1917, by a blow on the elbow from a stone. Pain was present for two months. Then the outline of the elbow was found to be altered by swelling around the joint. Motion was limited. The x-ray showed radiating bony deposits extending from the coronoid process of the ulna into the soft parts. A diagnostic incision showed an osteochondrosarcoma of the ulna.

The third patient was also a soldier, aged 36, wounded Jan. 20, 1918, in the same way as the soldier in the preceding case except that the wound was open. It healed in three weeks, and he regained use of the arm. Eight months later, when he presented himself, he had a tumor in the middle of the right thigh, a swelling which was hard and attached to the bone and fixed in the surrounding tissue. The x-ray also appeared to show a thickening of the cortex and new spicules of bone extending into the soft parts. Diagnostic incision showed a malignant tumor arising from the connective tissue composed of spindle cells with some osteoid material between them. Sebestyén<sup>90</sup> pointed out that although these tumors seemed to arise from the periosteum, morphologically it was possible that they arose from the endosteum or even from the bony substance itself, and that there is no more difficult task for a pathologist than judging correctly the exact point of origin of a sarcoma of the bone from microscopic sections.

These cases were considered by Sebestyén as of periosteal origin. He concluded that most of the traumatic sarcomas of the bones which follow a single direct injury are clinically of the periosteal type with a short latent period; while those due to open injuries, distortion or fracture and with a longer latent period, are more often sarcomas of the central myeloid type.

Paul Segond<sup>91</sup> discussed the statistical collections of case reports of tumors of alleged traumatic origin, and doubted that they have any value, quoting Auguste Comté to the effect that they represent only "empiricism under a mathematical disguise, for the most extensive statistics when they are derived from a variety of sources often have less value than fifteen minutes of good observation." Consequently, all that could be said, he thought, was that a tumor is produced by a trauma only rarely and then probably by the intermedium of a chronic process. He granted that even this intermedium is "easy to argue about and difficult to prove." He then went on to study a series of conditions somewhat aside from the main theme under discussion, but of general interest. He considered, for example, a person who already has a cancer

91. Segond: *Ass. franç. d. chir.* 20:745, 1907.

who receives a blow at a point distant from the cancer. Owing to his poor condition, the injury may be more serious than it would be to one in perfect health, and the question of some compensation may have to be considered. Again the blow may strike the tumor and aggravate it, or a spontaneous fracture sustained by a person while employed may be found to be due to a sarcoma of the bone. In a case cited, the French courts refused compensation, holding that the disease which caused the fracture did not have any relation to his work. Another situation arises when a person who has a scar, fistula, ulcer or old callus is injured at the site of such lesion, and ultimately develops a tumor there. In commenting on these three instances, Segond made mention of "attenuated liability." Finally, the question of compensation arises when the trauma produces a scar, fistula, ulcer or callus which much later and spontaneously becomes the site of a tumor. Under these circumstances, the trauma is certainly not a causative agent, but rather the patient's underlying constitution is; this is a vague notion, perhaps, but one expressing what every one recognizes. In most people, a cancer does not develop in a scar or in an ulcer, but rarely a malignant growth does appear. This difference in persons must be ascribed, pending further knowledge, to some peculiarity of the individual structure of the person. Such susceptibility to formation of tumors has been demonstrated in animals and is probable in man. Of its nature nothing is known. Compensation for this situation can scarcely be thought of.

The possibility that benign tumors may be converted into malignant ones under the influence of trauma is apparently remote, although a few types are believed to be more commonly susceptible to such a transformation than are the rest. It is doubtful whether an acute trauma has ever accomplished such a change. There is no doubt, on the other hand, that irritation of a chronic type applied to keratoses, to certain adenomatous tumors, such as polyps of the intestine, and perhaps to quiescent nevi, is often effective in bringing about such a change. Few pathologists, however, believe that circulatory changes lasting a few weeks, such as the exudation about a sprained joint, a carbuncle or a hematoma, is sufficient chronic irritation to produce a tumor. The irritation must be prolonged.

Frangenheim<sup>95</sup> was among those who believed that some tumors are changed from benign to malignant ones by outside irritants. Ewing<sup>90</sup> stated definitely that a single trauma had never in his observation changed a benign quiescent remnant of tumor cells into a malignant tumor. Such a statement would include the nevi, the hypernephromas, the mixed tumors of the salivary glands, the branchiogenic cysts and the neurofibromas. The case of Versé,<sup>92</sup> who described an extensive neuro-

92. Versé: *Med. Klin.* 18:1400, 1922.

fibromatosis occurring in father and son, puts undue emphasis on the trauma sustained by the father who injured one tumor on his foot. This tumor was excised but recurred in three years. In six years, a tumor appeared on the scalp, and the patient shortly died with neurosarcomatous metastases. It is impossible to attach much importance to the original trauma when the course of the case makes it obvious that the tumors were capable of becoming malignant without the trauma. Von Hanseemann<sup>93</sup> discredited the importance of irritation of nevi, stating that they are normally insensitive and hence are only scratched or rubbed by the patient after the malignant process has already begun.

*Metastases.*—It has been proved (Knox<sup>94</sup>) that repeated pressure in examination or massage may cause wide distribution of particles of a tumor; whether a single blow can accomplish the same is not known.

The question of the localization of metastases through trauma has been widely considered. Brinkmann<sup>95</sup> recently reported a patient with a bone tumor resembling thyroid tissue and supposed to have been localized as the result of a fall. Lubarsch<sup>96</sup> by experiments on mice showed that the localization of metastases, as in the liver, can rarely be determined by a single injury. He also said that this could be assumed to be true only if the localization is in an unusual site and the trauma is sufficiently severe to cause cells of the tumor to enter the veins. He regarded injuries caused by crushing or shaking as the most effective. He further attempted to induce metastases in the bones of mice with inoculated tumors by fracturing one of the long bones; but these experiments were consistently negative. Jones and Rous<sup>97</sup> showed in animals that injury to the peritoneum can permit localization of particles of a tumor. In their opinion the injury causes a rapid reparative process in the subendothelial connective tissue and such rapidly proliferating highly cellular tissue elaborates the supporting and nutritional stroma which facilitates the growth of the tumor cells. This may also be valid in other situations.

#### SUMMARY AND COMMENT

The question of the traumatic etiology of tumors therefore appears to have been largely excluded by most pathologists so far as is meant a direct exciting and essential cause. Von Hanseemann,<sup>93</sup> Gruber<sup>98</sup> and Pick<sup>81</sup> pointed out that after all the injuries sustained in the war no greater number of tumors could be observed in the war veterans, even

93. Von Hanseemann: *Handbuch der Aertzlichen Erfahrungen im Weltkriege*, 1921, vol. 8, p. 53.

94. Knox, L. C.: *Ann. Surg.* **75**:129, 1922.

95. Brinkmann, E.: *Klin. Wehnschr.* **6**:1903, 1927.

96. Lubarsch: *Med. Klin.* **8**:1651, 1912.

97. Jones, F. S., and Rous, Peyton: *J. Exper. Med.* **20**:404, 1914.

98. Gruber: *Ztschr. f. urol. Chir.* **13**:66, 1923.

in those who were of an age at which sarcoma most frequently occurs, than in civilians. Ten years have now elapsed, and an increase in the incidence of tumors has not been noted in the population of any of the combatant nations.

Pick<sup>31</sup> especially regarded his opportunity with the army of the western front as affording a mass of homogeneous experimental material and believed that if sarcoma could result from external injury he should see many cases in his service at that time, since the age of the soldiers corresponded with the period of frequency of sarcoma. Only two cases of sarcoma appeared which he could even suspect of arising from war injuries.

In 1918, the French Association for the Study of Cancer was requested to report on the relationship between traumas and tumors in the light of the experience obtained during the war. A number of important pathologists and clinicians discussed the problem and practically all except Bérard thought that traumas had practically nothing to do with the appearance of tumors. Bérard<sup>34</sup> had already reported favorably on the possibility of such an influence.

Forgue<sup>99</sup> showed that the regional distribution and the age distribution in 536 cases of cancer were practically proportional to the like distribution in the male population not in the service.

Von Hanseemann,<sup>93</sup> also, pointed out that not only has an increase in tumors not appeared following the war, but new types have not appeared.

Löwenstein,<sup>100</sup> in his military service extending from 1889 to 1917, also calculated that among the young men whom he had observed the percentage of sarcoma arising in such a group should be 12 per cent, but he was unable to report any such percentage.

Eunike,<sup>101</sup> also, observed six examples of sarcoma of the bone which he believed might possibly be due each to a single trauma, but stated that the rarity of such lesions shows that other influences are essential to their production. His paper is one of the best on the subject, and shows judicial handling of a series of interesting and carefully studied individual cases.

Brosch<sup>102</sup> stated that a single trauma preceding a pathologic process could not cause a tumor, but that the early productive and reparative changes observed in scars were essential forerunners of the neoplastic process and that this accounted for the inability of experimenting pathologists to produce tumors in normal tissues.

99. Forgue: *Bull. d'ass. franç. p. l'étude du cancer* 7:555, 1914-1918.

100. Löwenstein, quoted from L. Pick: *Med. Klin.* 17:416, 1921.

101. Eunike, K. W.: *Deutsche Ztschr. f. Chir.* 151:262, 1919.

102. Brosch, A.: *Virchows Arch. f. path. Anat.* 162:32, 1900.



Goebel<sup>103</sup> also stated frankly that a single injury never caused a malignant tumor, but that chronic irritation, repeated injuries and scar tissues indirectly, but not entirely mechanically, might have done so. The thermal and chemical reactions consequent to the other pathologic processes were essential. Oberndorfer<sup>104</sup> also asserted dogmatically that trauma could not independently cause proliferation of normal cells; that some underlying predisposition must be present.

Frangenheim<sup>65</sup> was inclined to believe that trauma might have had some relation in some cases but that it could not be a primary or chief cause because of the large number of tumors in new-born infants and other infants who had not suffered traumas.

Virchow,<sup>105</sup> also, while admitting the fact that the influence of trauma could not be dogmatically denied, required that there should be some as yet unknown predisposing factor in the patient and also that the trauma must have been implanted on pathologic tissues.

Ribbert<sup>24</sup> consistently opposed the theory that a trauma could cause a tumor but admitted that, although positive proof was lacking, the possibility must be conceded. He denied ever having seen a clearly demonstrated case.

Jordan,<sup>106</sup> in discussing the origin of tumors from single traumas, held that "in regard to the current hypotheses of tumor formation following injury we possess no information concerning the actual rôle played by trauma." Further, he pointed out that the time required for the development of a tumor is in general unknown and he called attention to the fact that after the extirpation of a carcinoma many years might elapse before metastases make their appearance. Again he stated that as tumors arise from small groups of cells "we are never in a position to deny that a small tumor may have preceded the trauma which is alleged to have caused it." Nevertheless, he granted that in the law "possibilities and probabilities" have to be considered and that compensation might be proper when the injury had caused a hitherto unrecognized tumor to grow rapidly and thus become evident.

Theilhaber,<sup>107</sup> whose conclusions in general were compiled without critical study, convinced himself of the importance of atrophied scars as a prerequisite to the formation of tumor tissue. This is one of the hypotheses which can apply only to small groups of tumors in any case

103. Goebel: *Sammlung klinische Vorträge*, Leipzig, 1905, p. 403; *Chirurgie*, no. 110, 209.

104. Oberndorfer: *Aerzt. Sachverst.-Ztg.* **13**:32, 1907.

105. Virchow: *Die Krankhaften Geschwülste*, Berlin, 1863.

106. Jordan: *München. med. Wchnschr.* **48**:1741, 1901.

107. Theilhaber, A.: *Deutsche Ztschr. f. Chir.* **110**:77, 1911; for complete bibliography of writer's own publications see *Die Entstehung und Behandlung der Karzinome*, Berlin, 1914.

and has little bearing on the question of acute trauma, as no one supposes that sarcomas of the bones in young people have any relation to old scars in the periosteum or bone.

Versé,<sup>92</sup> also, stated that there must be a general and a local disposition to the formation of tumor, a statement so general as to afford one little conception of what is meant.

Sauerbruch<sup>46</sup> and Ewing<sup>80</sup> were both of the opinion that the anatomic flexures, angles and points of greatest mechanical and chemical stress are the ones in which tumors are most likely to develop—this again being a generalization scarcely related to the subject since the trauma referred to is repeated and persistent.

Borst<sup>108</sup> did not feel that trauma could be entirely excluded, because of the difficulty of explaining obscure cases. But why explain the inexplicable by a new hypothesis? He by no means accepted traumas, however, as a general cause of tumors, but like Pick,<sup>31</sup> Eunike<sup>101</sup> and Ewing<sup>80</sup> was willing to admit the possibility of occasional cases differing from the rest.

Hauser and Beneke,<sup>109</sup> also, noted that the distribution of tumors in general showed that traumas could not be the only cause; for example, the large number of malignant tumors of the breast as compared with the small number in the extremities, where trauma, it is admitted by all, is sustained the more frequently. Roger Williams<sup>110</sup> regarded this as an important argument against the traumatic theory, and declared that men sustain three times as many injuries to the breast as women, but that they suffer from carcinoma of the breast in the proportion of one man to 116 women.

It is therefore evident that any critical observer influenced by the leaders in pathologic thought will hardly consider trauma to be a general cause of any type of tumor. Some pathologists, as has been pointed out, admit it as one of the factors which might act at a favorable moment in an individual with some local or general susceptibility to tumor, and so be an important contributory cause. Even as to this, Williams was emphatic in asserting that if trauma were a contributory cause one should see more cases of multiple neoplasms, since the soil on which the injuries of life were being inflicted was a proper one. The bilateral varicose carcinomas of the extremities are an instance of the importance of the individual predisposition when combined with a chronic irritant. Most observers believe the trauma to be only an external factor calling attention to a preexisting or subsequent but independently caused tumor.

108. Borst, quoted by Ziegler (footnote 33).

109. Hauser and Beneke, quoted by Ziegler (footnote 33).

110. Williams, Roger: *The Natural History of Cancer*, New York, 1908, p. 286.

The frequency of such unrecognized cancer has been clearly brought out by Wells,<sup>111</sup> who showed that as the diagnostic error in cases of cancer as revealed by necropsies in various hospitals is from 25 to 40 per cent, the percentage of error in diagnosis among the population at large must be much greater. Probably 50 per cent of the neoplasms in some communities are never diagnosed. It is evident that with so large a group of persons whose cancers never are recognized, there are ample opportunities for an accidental trauma to be considered as a causative agent. If the current reported death rate from cancer in the United States is taken as about ninety per hundred thousand, the unrecognized cases can scarcely be less than forty, as but proportionately few autopsies are performed in this country. This makes the true death rate probably 130 per hundred thousand, or about that of Switzerland, where a large proportion of those dying are given postmortem examination. As the average life of a patient with cancer has been computed to be about two years, there should be in the population as a whole some 250 persons to the hundred thousand who have cancer in some stage, in addition to those who are to die within the year and are so recorded. In other words, besides those evidently dying of the disease, one person in 400 of the whole population may have a cancer in some stage of development. As sarcoma forms about one tenth of the total number of malignant growths, one person in 4,000 may have such an unrecognized sarcoma. The opportunity for a trauma to call attention to such a condition is evidently considerable and must be recognized in any study of the relationship between injury and the production of a sarcoma. This is the type of tumor which the majority of those who believe in the traumatic origin of malignant growths consider to be most frequently produced by injury.

Lewy<sup>112</sup> also showed from the records of the New York State Industrial Compensation Bureau that the frequency of malignant tumors among injured persons was about one to 700, or approximately that of the general population at the age of 50.

Another basis for exclusion of the theory is the statement made by Williams<sup>110</sup> that men are more subject than women to trauma, and this is no doubt true for the more severe injuries, such as fractures, sprains and dislocations. In his material, men have fewer cases of malignant cancer than women, in the proportion of 1 to 1.7. The difference in these figures is chiefly due to the frequency of carcinoma of the internal organs and not to sarcoma alone and so it is not such an effective argument as it first appears.

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111. Wells, H. G.: Relation of Clinical to Necropsy Diagnosis in Cancer and Value of Existing Cancer Statistics, *J. A. M. A.* 80:737 (March 17) 1923.

112. Lewy, R.: New York State Department of Labor Med. Bull. no. 1, 1923.

Perhaps a better practical summary of the facts has not been made than that by Lubarsch,<sup>7</sup> who on the basis of wide pathologic experience reminded us:

1. That blows and other injuries generally call attention to hitherto unsuspected tumors, and that proof of the existence of such unsuspected growths is given by the fact that neoplasms which have never given recognizable symptoms are constantly being discovered at autopsies.
2. That injuries are infinitely more frequent than neoplasms.
3. That many tumors have a long latent period.
4. That experimental evidence for the theory that a single trauma can cause a tumor is lacking.

#### CONCLUSIONS

1. A careful perusal of the more important literature on the relationship of a single trauma to a tumor leads inevitably to the conclusion that a causative relationship between the two has never been completely established.

2. A few examples, such as have been cited in this paper as worthy of note, suggest the possibility that a single trauma may induce a tumor, though only in a limited number of situations, but proof even of these few instances is lacking.

3. This causative relationship never can be established until it is demonstrated by experimental methods that a single injury can regularly produce a tumor.

4. The award of compensation solely on the basis of the production of a tumor following a single trauma is, therefore, unjustifiable.

5. The award of compensation on the basis of a trauma acting as a collateral or adjuvant agent by causing chronic irritation which in time produces a tumor, or on the basis of a fracture or other injury in a bone already involved by cancer, or on the basis of violence determining a metastatic site for a cancer already present in the body, or, in exceptional instances, stimulating a tumor to greater activity of growth, may be justifiable if proof of the injury is received and proof of the presence of a tumor is made by the microscope.

6. Many of the recorded cases in which compensation has been awarded are instances of trauma merely calling attention to a pre-existing tumor, either in the skeleton or in the organs or the connective tissues. And in the mere presence of such a tumor a valid basis for compensation does not exist. The frequency of such preexisting and unrecognized tumors is shown by the fact that routine postmortem examinations increase by at least one fourth the percentage of cancer found by diagnosis on the living patients in institutions offering the best diagnostic facilities.



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The literature contains numerous other papers not cited here but referred to in the bibliographies of the papers that are listed in the course of this review. Many of these are reports of single cases which are too brief or too incomplete to be of value; others are of interest but do not add new facts or theories to those quoted.

## Notes and News

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**Chicago Meeting of Pathologists and Bacteriologists.**—The annual meetings of the American Association of Pathologists and Bacteriologists and the affiliated societies, namely the American Association of Immunologists, the American Association for Cancer Research and the Medical Museums Association, will be held in the new laboratory of pathology of the medical school of the University of Chicago on March 27, 28 and 29, 1929. This new laboratory building has been occupied by the department of pathology of the University of Chicago since Oct. 1, 1927, and constitutes the center section of the new medical group of the University of Chicago. As shown in the accompanying illustration, it is



New laboratory of pathology, University of Chicago.

a connecting building between the medical clinic and the surgical clinic, and forms the central portion of the south side of Medical School Court, thus making it the central part of both the hospital and the preclinical laboratories. It contains 886,000 cubic feet, with 56,412 square feet of floor space, distributed in six floors and a basement. There are twenty private rooms for research workers, as well as five larger laboratories for research work, in addition to three laboratories for class work, three class rooms, a large lecture room, an autopsy amphitheater, and two smaller autopsy rooms, a display museum, a storage museum, a large medical library reading room and numerous storage, preparation and office rooms. The entire upper floor is occupied by animal quarters. The laboratories are entirely for the use of the department of pathology, hospital and clinical laboratory work being done in the clinic buildings. Part of the work of the Otho S. A. Sprague Memorial Institute is also conducted in this building, in conjunction with the department of pathology.

**Cooperative Blood Donor Bureau in New York.**—Through the activities of the committee on blood groups of the National Research Council, a committee of interested persons, under the chairmanship of Dr. Arthur F. Coca, has established a central agency under cooperative supervision for supplying blood donors to hospitals in New York City. At present, the bureau, which is practically self supporting, is serving about twenty hospitals. It is planned to form a corporation, consisting of the superintendents of the hospitals concerned, to manage the bureau, which will be conducted under the immediate supervision of physicians connected with the cooperating hospitals. The Board of Health of New York City has taken under consideration the formation of regulations for the control of agencies supplying blood donors.

**International Nomenclature of Blood Groups.**—In 1927, the American Association of Immunologists recommended the general adoption of the designation of the human blood groups by letters as suggested by Carl Landsteiner, who discovered blood grouping in 1900. In the order of frequency of the groups in this country and Europe, these designations are: O, universal donor; A, formerly group II; B, formerly group III; AB, universal recipient. The designations represent iso-agglutinogens A and B. This nomenclature is coming into use everywhere, more and more; it has been approved by the committee on hygiene of the League of Nations and is official in the United States Army and Navy. The ARCHIVES requires its use in the papers and abstracts it publishes concerning the blood groups.

## Obituaries

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ALEXANDER A. MAXIMOW, M.D.

1874-1928

Alexander Maximow was born Jan. 22, 1874, in St. Petersburg, Russia. From 1882 until 1891, he attended the German gymnasium of Karl May; he graduated in 1891. In the same year he entered the Imperial Military Medical Academy at St. Petersburg. Here, as a student, he showed a keen interest in morphologic problems. For his work on the experimental production of amyloid he was given a gold medal by the academy. He passed the examination of this institution in 1896, with special honors. The next three years he spent in the department of pathology. In 1899, after defending his thesis "On the Question of the Pathological Regeneration of the Testis," the degree of M.D. was conferred on him by the academy. The years 1900 and 1901 he spent in Germany studying; first, he studied embryology under Hertwig in Berlin; he then went to Ziegler in Freiburg, where he completed the first of his classic studies on inflammation. On his return to St. Petersburg, in 1902, he was made Privat-Dozent in pathology, and in the following year he was chosen professor of histology and embryology. He held this position until 1922, when he left Russia and came to the University of Chicago as professor of anatomy. This chair he occupied until his death from angina pectoris on Dec. 4, 1928.

In keeping with his international reputation, he was a member of many scientific societies in this country and abroad.

His scientific work may be divided into four periods. During the first part of his scientific career, from 1896 to 1902, he published a series of papers on normal and on pathologic histologic questions. Some of these were purely descriptive—as on the histogenesis of the placenta—while others were of a more experimental nature. Among these were his studies on experimental amyloid, tissue emboli in the pulmonary arteries, on the pathologic regeneration of the testis and ovary and on the structure of, and the changes in, the salivary gland during secretion. These formed the fundamental, morphologic background of his future work.

The second period included a series of experimental investigations on the histogenesis of the connective tissue in inflammation. In the first of these, he classified the various cells in inflamed tissues and traced them to definite cell types of the normal connective tissue and blood. With great clearness, he elucidated the rôle played by the hematogenous

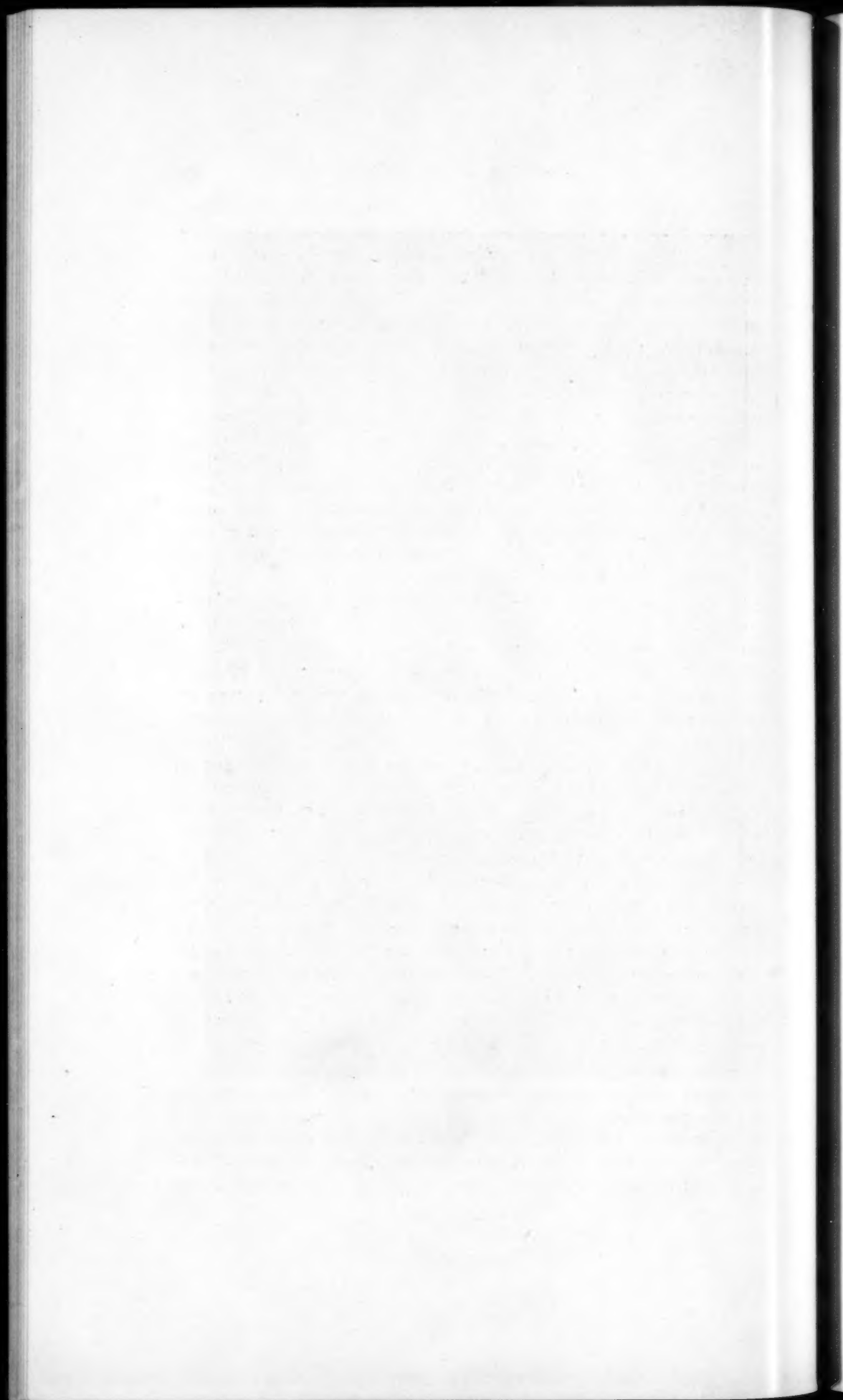




(Photograph supplied by Helen B. Webster studio)

ALEXANDER A. MAXIMOW, M.D.

1874-1928



and histogenous lymphoid elements in the production of the mononuclear exudate cells—which he called polyblasts—and later in the formation of the scar. He showed that the polyblasts were endowed with a much greater vitality and capacity for progressive development than had been known before his work. The results of this first monograph were developed and completed in a series of subsequent papers. At this time, he also published careful histologic analyses of the cells of the normal connective tissue.

The third period of his work can be looked on as a natural extension and expansion of the second period. From his previous studies he realized that a close relationship existed between the cells of the connective tissue and those of the blood. But the nature of these relationships was not clear, because of the confusion then reigning in morphologic hematology. He realized that the histologic investigation of the adult organism alone could not lead to a decisive solution of these problems. He accordingly began his classic, histogenetic studies of the embryologic development of the blood and connective tissue. Some of these were published in a series of ten papers under the title of "Studies on Blood and Connective Tissue." In these, the first stages of the embryonic development of blood and connective tissue cells and the histogenesis of the bone marrow and thymus were studied in mammals, amphibians and selachians. He also demonstrated the morphologic characteristics and differences of the hematogenous and histogenous mast cells.

In this period, he succeeded, moreover, in proving the development of all blood cells from a common mother cell—which he identified with the lymphocyte—in the kidney, after ligation of the blood vessels of this organ. He thus confirmed the unitarian theory of hematopoiesis, of which he was one of the leading proponents.

The last period of his scientific work was devoted in great part to investigating the prospective potencies, interrelationships and histogenesis of the mammalian blood and connective tissue cells by the method of tissue culture. By using this method, he was able to produce further confirmatory evidence of the fact that lymphocytes of the blood, as well as of lymph nodes, are undifferentiated cells. He was able to observe their transformation into myelocytes and, under different conditions, into polyblasts and later fibroblasts. In his last experiments—of which he had published only preliminary notices—he was able to trace the purely extracellular origin of argyrophile and collagenous fibers in tissue cultures.

In 1927, he published, in von Möllendorff's "Handbuch der Mikroskopischen Anatomie," a very complete monograph on the connective and blood forming tissues. It is richly illustrated by the careful, lifelike

drawings which have made all of his papers valuable, objective contributions to the various subjects he investigated. This monograph also comprises a critical survey of practically the entire literature on this subject and contains excellent summaries of the leading hypotheses, theories and facts in this highly controversial field.

He always spoke of himself as a "simple morphologist," but in the same breath he maintained that there are many problems which as yet, by their very nature, can be investigated only by morphologic methods. He demanded of his students and of the other workers in the fields under investigation an exceedingly high standard of histologic preparations. His own slides were universally acknowledged to be of a superior quality.

The descriptions in all his papers, both verbal and pictorial, are highly objective. He drew the simplest conclusions deducible from his observations. When new facts became established in his own or another's work, he never hesitated to acknowledge his previous errors and to change his theories accordingly if necessary. But, withal, he was highly critical, and demanded clearcut proof from others as well as of himself.

In addition, it must be pointed out that Dr. Maximow was an inspiring, stimulating teacher, particularly to those of us who have had the privilege of working intimately with him in his laboratory. One should also not lose sight of the fact that he was one of the outstanding general histologists of his generation. To this bear witness not only his previously mentioned writings, but also his Russian textbook on the "Principles of Histology," in two volumes, and his nearly completed American textbook.

No matter what the future brings in the way of interpretation and elucidation of the many problems investigated by him, particularly in the field of the blood and connective tissue, of this much I am sure, that the observations of Alexander Maximow, made with the best experimental histologic methods of his time, will stand. For many years to come, his work will offer a firm base for further work on questions involving the normal and pathologic histology and histogenesis of the blood and the connective tissue—a field which he made so strikingly his own.

WILLIAM BLOOM.







JOSEPH GOLDBERGER  
1874-1929

JOSEPH GOLDBERGER, M.D.

1874-1929

Dr. Joseph Goldberger of the United States Public Health Service died at the Naval Hospital, Washington, D. C., on Jan. 17, 1929, following an illness of several weeks. In his death, his profession has lost one of its ablest scientists; and the loss to the country is irreparable.

Dr. Goldberger was born in Austria Hungary on July 16, 1874, and came to the United States with his parents when but a boy. He received his academic education in the public schools of New York and graduated from Bellevue Hospital Medical College. After several years in hospital and private practice, he entered the United States Public Health Service in July, 1899, as an assistant surgeon; he was promoted to the grade of passed assistant surgeon in 1904, and to the grade of surgeon in 1913. His early work included assignments to general medical, quarantine and epidemic diseases. The last mentioned assignments were to epidemics of yellow fever at Tampico, Mexico; Ponce, Porto Rico; Vera Cruz, Mexico, and New Laredo, Texas. At Tampico, he contracted yellow fever during the conduct of his duties. In 1905, he performed highly valued field work during the epidemic of yellow fever in the South.

Dr. Goldberger's special qualifications for scientific research were early recognized. He was accordingly attached to the Hygienic Laboratory, Washington, D. C., in the fall of 1904, from which institution he conducted his investigations of many public health problems. While he was attached to the laboratory, this work involved prolonged absences and extensive travel, sometimes emergency studies. The latter studies related to dengue fever in south Texas, where he contracted the disease in 1907; to an epidemic of diphtheria in Detroit in 1913, and to straw mite disease in New Jersey, the cause and methods of transmission of which he discovered.

The most notable studies of Dr. Goldberger related to measles, typhus fever and pellagra, all of which are major problems, from a public health standpoint. In association with a colleague, he was able to transmit measles to lower animals, throwing light on the period of incubation and infectivity of the disease.

During the winter of 1909-1910, in association with another officer, he studied typhus fever in Mexico City, and contracted a severe attack of the disease. During the winter of 1911-1912, he again carried on studies of typhus fever in Mexico, which were of the greatest importance because they demonstrated the identity of the typhus fever of Mexico and Brill's disease, a mild form of typhus known to prevail in New York and certain other places in the United States for many years.

He also demonstrated that typhus fever is transmitted not only by the body louse, but by the head louse, information of the greatest value in the prevention of this epidemic disease.

By far the most important work conducted by Dr. Goldberger, however, related to pellagra. This he began in 1913 and vigorously prosecuted until the time of his last illness. In these studies, he was able to utilize his special training and experience in bacteriology, epidemiology and zoology. No scientific worker has been able to approach this problem from as many angles. As a result, he soon became convinced that it was a nutritional disease, due to an unbalanced diet. He set himself the important task of determining, if possible, what features of diet were lacking. The volume of work and the mass of detail have been tremendous. Fortunately, he was able to report advances from time to time. By epidemiologic methods, among children in institutions, he demonstrated conclusively that pellagra is a dietary disease. By extensive feeding experiments, he proved that it is not an infectious disease, and he actually produced the disease in man by a diet which he had concluded was the essential factor of causation. The actual factor necessary for the prevention of the disease he identified, but not in the pure state, and called it pellagra preventive. As a result of his researches, he determined the relative preventive value of this factor in different foods and actually found that by the use of proper diets pellagra could be not only cured but prevented. In connection with this work, he likewise determined that "black tongue" of dogs is a dietary disease closely akin to, if not identical with, pellagra, and he was able to determine symptoms of pellagra in other laboratory animals by feeding, all of which has had a potent influence in stimulating further wide researches in nutrition. Pellagra was first recognized in the United States in 1907. By 1909, it had become a menace to a considerable section of the public. As a result of Dr. Goldberger's studies and the prompt utilization of his results by physicians, pellagra is now an entirely preventable disease. Certainly, no more valuable public health research has been conducted in any country within a generation than these studies in pellagra. This disease had existed and been recognized in the old world for 100 years, but almost immediately after its discovery in the new world, it was attacked and the solution for its prevention was determined. In the performance of this great work, Dr. Goldberger has erected a lasting monument to himself; the generations to follow will be debtors to the work and achievements of this great man.

Dr. Goldberger leaves to his family an illustrious name. He was married to Mary Farrar of New Orleans. They have four children, some of whom have grown to manhood.

R. C. WILLIAMS.



## Abstracts from Current Literature

### Experimental Pathology and Pathologic Physiology

THE EFFECTS OF CARBON ARC RADIATION ON THE BLOOD OF DOGS. H. S. MAYERSON and H. LAURENS, *Am. J. Physiol.* **86**:1, 1928.

Following a single exposure (abdominal) to carbon arc radiation, there was observed in dogs a temporary increase in plasma volume of from 6 to 37 per cent, with recovery to normal in five hours. Further exposures caused recurrence, but not augmentation, of this dilution; the duration, however, varied with the strength of exposure and the interval between successive exposures. After massive exposures, the initial dilution was followed by a slight concentration. Repeated exposures resulted in a stimulation of the hematopoietic system, indicated by an increase in the red cell count of from 10 to 19 per cent, lasting from three to six weeks. The red cells during the postradiation period were smaller and less saturated with hemoglobin. Blood platelets diminished in number and volume during irradiation, usually with recovery within five hours. Occasionally there was an increase during the postradiation period. A progressive leukopenia, with a marked lowering of the white cell count during the postradiation period, developed during irradiation.

H. E. EGGERS.

THE INFLUENCE OF "HEAT" ON THE SURVIVAL PERIOD OF DOGS AFTER ADRENALECTOMY. J. M. ROGOFF and G. N. STEWART, *Am. J. Physiol.* **86**:20, 1928.

"Heat" in dogs was found to be associated with a marked lengthening of the survival period following suprarenalectomy, and of the period of good health. All survived longer than did any of the more numerous control animals.

H. E. EGGERS.

THE EFFECT OF LIGATION OF THE COMMON BILE DUCT UPON THE APPEARANCE OF TETANY IN THYROPARATHYROIDECTOMIZED DOGS. J. C. BROUGHER, *Am. J. Physiol.* **86**:39, 1928.

In dogs, ligation of the common bile duct, with or without cholecystectomy, prevents the development of typical parathyroid tetany. This may occur in mild form, in which case its onset is delayed. This delay may be explained in several ways: a lessened excretion of calcium which would otherwise occur in the bile; increased absorption of calcium from the intestine because of the absence of the alkaline bile salts, by which calcium is precipitated, and depression of the central nervous system by the absorbed bile.

H. E. EGGERS.

THE SEASONAL VARIATION IN BASAL METABOLISM. F. L. GUSTAFSON and F. G. BENEDICT, *Am. J. Physiol.* **86**:43, 1928.

Monthly measurements were made of the basal metabolism of twenty young women, with the exception of the months of July, August and September, for a period covering fifteen months. While the determinations varied with stimuli incident to college life, the average values suggested that the rate was at a low level during the winter months, rising during the spring and summer. Many of the results suggested that there is a lowering of metabolic rate during menstruation.

H. E. EGGERS.

NORMAL MENSTRUATION AND GASEOUS METABOLISM. F. G. BENEDICT and M. D. FINN, *Am. J. Physiol.* **86**:59, 1928.

A series of intermittent determinations of basal metabolism made on one woman over a period of twelve years showed an average deviation from the predicted

(Harris-Benedict) heat production of  $-4.5$  per cent for eighty-nine intermenstrual days, and  $-7.5$  per cent for thirty-two menstrual days. The lower metabolism during the menstrual period was confirmed by the additional observation that the preponderance of deviations greater than  $-10$  per cent occurred on menstrual days. A similar conclusion was suggested by a series of monthly determinations on twenty college students. Finally, a series of daily observations were made on the first subject, which showed in general that oxygen consumption was lowest and most uniform during the menstrual period, and highest about one week after its cessation.

H. E. EGGERS.

HEMORRHAGIC HYPERGLUCEMIA. M. G. MULINOS, *Am. J. Physiol.* **86**:70, 1928.

In cats anesthetized with iso-amyl-ethyl barbituric acid arterial hemorrhage was found to yield blood increasingly rich in reducing substances. That this was not due to the asphyxial outpouring of epinephrine was shown by its occurrence in suprarenalectomized animals. A coincident fall in hemoglobin showed that the hemorrhage had a marked diluting action on the blood, from which the writer deduces that the diluting fluid contains at least as much dextrose as the blood itself.

H. E. EGGERS.

THE EFFECT OF VERY EARLY ABLATION OF THE CORPUS LUTEUM UPON EMBRYOS AND UTERUS. G. W. CORNER, *Am. J. Physiol.* **86**:74, 1928.

Recently pregnant rabbits, from fourteen to twenty hours after mating, were subjected to complete or partial oophorectomy, with complete or partial removal of the corpora lutea. In the case of complete oophorectomy, there was a failure of the endometrium to develop the changes characteristic of pregnancy, and the blastocytes died soon after entering the uterus. With removal of one ovary and damage to the other, but with survival of one or more corpora lutea, the developments were those of normal pregnancy; after removal of all the corpora lutea, with survival of a portion of ovarian tissue, there was a lack of endometrial development and of that of the ova. The experiments confirm the existence of progestational proliferation of the rabbit's uterus, and support the view that this is dependent on the corpora lutea. They also confirm the view that the corpora lutea are necessary for embryonic implantation, and they suggest that normal implantation is dependent on the progestational proliferation of the endometrium. This same proliferation appears to be necessary to the survival of the free blastocytes during the three or four day interval before the ovum becomes implanted, after its arrival in the uterus.

H. E. EGGERS.

CHANGES IN HEMOGLOBIN FOLLOWING REMOVAL OF THE SPLEEN. G. B. RAY, *Am. J. Physiol.* **86**:138, 1928.

Determinations were made of the red cell count, total blood pigment and functional hemoglobin in dogs following splenectomy. With the use of the term "nonfunctional pigment" to express the difference between total pigment and hemoglobin, the amount of this present at various times after the operation afforded a physiologic index of the damage following splenectomy. It paralleled neither the red cell count nor the total blood pigment, so that these cannot be regarded as criteria of functional changes in the blood in this condition.

H. E. EGGERS.

THE POLYCYTHEMIA OF ACUTE ANOXEMIA AND ITS RELATION TO THE SYMPATHICOADRENAL SYSTEM. J. J. IZQUIERDO, *Am. J. Physiol.* **86**:145, 1928.

Although brief asphyxia caused by mechanical obstruction causes a prompt polycythemia in normal animals, this effect is probably to be regarded as largely due to the excitement of the animal. If, though, asphyxia is caused by a gradual

lowering of oxygen tension, the element of excitement may be avoided; in cats in these circumstances there may be no excitement, but the animals will react with rapid and shallow respiration, salivation, erection of hair and polycythemia. The last is absent in splenectomized animals. With animals in which the spleen was denervated about one week before the experiment, there may be an anoxemic polycythemia greater than that of the normal animal. Since this disappears if the suprarenals are demedullated, it is probably to be ascribed to the extra epinephrine acting on the toneless spleen. Increase of carbon dioxide in the inspired air was without effect in polycythemia.

H. E. EGGERS.

THE EFFECT OF VARIATION IN POSTURE ON THE OUTPUT OF THE HUMAN HEART. A. GROLLMAN, *Am. J. Physiol.* **86**:285, 1928.

Determinations of the circulatory minute volumes of normal men and women in recumbent, sitting and erect postures showed postural variation to be without effect. However, as in the sitting, and even more in the recumbent position there is a decidedly lower vital capacity of the lung, with a lowering of the reserve air by a liter or more, much more time is required in those conditions to bring about thorough gas mixture. The maintenance of constant circulatory rate is explained by three chief factors: the maintenance of tone by the splanchnic area, the increased cardiac action with rise of rate and of blood pressure and the effect of respiratory changes. Fainting in the normal person is explained as occurring in the erect posture with muscular rigidity, so that the imperceptible but constant muscular movements which ordinarily force the blood past the valves of the veins are lacking.

H. E. EGGERS.

THE PENETRATION OF ULTRAVIOLET RAYS INTO LIVE ANIMAL TISSUE. W. T. ANDERSON, JR., and D. I. MACHT, *Am. J. Physiol.* **86**:320, 1928.

The passage of ultraviolet light, of wave lengths of from 2,537 to 3,000 Angstrom units, was studied in the partially detached, but living, skin of the rabbit by means of fluorescent photometry. It was found that there was a transmission of from 6 to 10 per cent through a skin 1.2 mm. thick. With the onset of death of the skin, there was definite reduction in transparency, and dead skin of the same thickness was found to be practically opaque to ultraviolet light shorter than 3,660 Angstrom units.

H. E. EGGERS.

OBSERVATIONS UPON ADRENALECTOMIZED CATS TREATED WITH THE CORTICAL HORMONE. F. A. HARTMAN, F. R. GRIFFITH, JR., and W. E. HARTMAN, *Am. J. Physiol.* **86**:360, 1928.

In suprarenalectomized cats treated with extracts of suprarenal cortex, a condition was observed simulating that of chronic suprarenal insufficiency. In general, the symptoms were like those of acute insufficiency, but with much more gradual development. In the majority of treated animals, the metabolic rate remained within normal limits for from seven to twenty-nine days after the removal of the second suprarenal. The animals never gained weight and usually lost long before the appearance of terminal symptoms. They were less resistant to cold and to infection, and fatigued more readily than normal animals. Overeating caused a rise of blood urea, and brought on symptoms of suprarenal insufficiency. A darkening of the skin was occasionally observed, and in one cat which survived 300 days there was a chocolate discoloration of the subcutaneous fat. The survival period was not influenced by thyroidectomy and gonadectomy.

H. E. EGGERS.

A COMPARATIVE STUDY OF THE ACID-BASE EQUILIBRIUM OF BILATERALLY NEPHRECTOMIZED AND ADRENALECTOMIZED DOGS. W. W. SWINGLE, *Am. J. Physiol.* **86**:450, 1928.

In bilaterally nephrectomized dogs there was no development of acid intoxication. While there was an occasional slight fall in alkali reserve, there was a

striking contrast to the acidosis of suprarenalectomy. A slight increase was found in blood sugar, in contrast to the marked fall observed after suprarenal extirpation. Increase in inorganic phosphates, sulphates and urea was found to follow both nephrectomy and suprarenalectomy. Following nephrectomy, there was a fall of blood chlorides. It is suggested that the acid intoxication of suprarenal insufficiency, and probably of uremia, is of extrarenal origin, since it was not present in nephrectomized dogs with total suppression of renal function.

H. E. EGGERS.

THE ACID INTOXICATION OF ADRENAL INSUFFICIENCY IN DOGS. F. M. YONKMAN, *Am. J. Physiol.* **86**:471, 1928.

In suprarenalectomized dogs there was observed a gradual rise of the inorganic phosphorus of the serum, increasing with the symptoms of suprarenal insufficiency. With the first signs of weakness, there is a decline of blood sugar. After this a fluctuation may occur, but there is an invariable terminal drop. The carbon dioxide capacity gradually decreases with the onset of symptoms. The  $p_H$  remains normal until the carbon dioxide capacity falls from 30 to 33 per cent by volume. After this it declines in company with the carbon dioxide capacity, indicating a shift from a compensated acidosis with normal  $p_H$  and low carbon dioxide capacity to an uncompensated condition. The acidosis is due in part to retention of phosphates and sulphates. That there is diminished renal output was indicated by functional tests.

H. E. EGGERS.

ACCUMULATION OF BILE AROUND THE LIVER. WALTMAN WALTERS and JESSE L. BOLLMAN, *J. A. M. A.* **91**:239, 1928.

The postoperative accumulation of bile around the liver, producing its displacement, is sufficient to cause symptoms of shock and even death if allowed to persist. From our experiments we believe the reaction to be due to interference with the circulation in the inferior vena cava from the downward displacement of the liver. Removal of the forces producing the displacement is followed, both clinically and experimentally, by the immediate return of normal circulation and the disappearance of symptoms. Bile accumulating around the liver is rapidly absorbed by the lymphatics of the diaphragm, and experimentally is detected in the lymph of a thoracic duct fistula in from two to three minutes after its contact with the peritoneal surface of the diaphragm. This is in contrast to the relatively slow appearance of bile in fluid from such thoracic duct fistulas when there is bile below the liver.

AUTHORS' SUMMARY.

THE HORMONE TEST FOR PREGNANCY. A. C. SIDDALL, *J. A. M. A.* **91**:779, 1928.

The test is based on the effect of the blood serum of pregnant women when injected into white female mice. The positive result consists either in enlargement with increase in weight of the uterus or ovaries of the mice. This test may prove of value in standardizing commercial preparations purporting to contain hormones that act on sex organs. In 142 cases of pregnancy the hormone test proved to have a high degree of accuracy.

THE EFFECT OF INSULIN ON PROTEIN METABOLISM. V. C. KIECH and J. M. LUCK, *J. Biol. Chem.* **78**:257, 1928.

The administration of insulin to the white rat appears to disturb the normal equilibrium between the rate at which its proteins are hydrolyzed and the rate at which the hydrolytic products are in turn degraded to urea.

ARTHUR LOCKE.



THE RELATION OF COPPER TO THE HEMOGLOBIN CONTENT OF RAT BLOOD.  
J. S. MCHARGUE, D. J. HEALY and E. S. HILL, *J. Biol. Chem.* **78**:637, 1928.

A dietary source of copper is essential to the maintenance of a high hemoglobin level.

ARTHUR LOCKE.

INFLUENCE OF LIGHT ENVIRONMENT ON THE GROWTH AND NUTRITION OF  
NORMAL RABBITS WITH ESPECIAL REFERENCE TO THE ACTION OF NEON  
LIGHT. WADE H. BROWN, *J. Exper. Med.* **48**:31 and 57, 1928.

The influence of light environment on the growth and nutrition of normal rabbits was studied by comparing the weight curves of animals living under different environmental conditions for periods of from four to eight months and the effects of change from one environment to another. Prolonged exposure to neon light was compared with confinement in the dark and exposure to diffuse, filtered sunlight of varying intensity. The results of the experiments showed that growth and nutrition were greatly affected by the light environment in which the animals lived. The effects produced by a given environment varied with the color or breed of the animal and appeared to be out of proportion to the differences in the intensity of the light or the energy represented. In a series of experiments dealing with the influence of light environment on normal rabbits, the growth of hair over shaved areas was used as an index of functional activity. The conditions compared were exposure to neon light, complete exclusion of light and exposure to diffuse, filtered sunlight of varying intensity. It was found that prolonged existence under these conditions affected the proliferative activity of hair follicles in a manner and to an extent comparable with the effects produced by the same environmental conditions on the growth and nutrition of the animals themselves.

AUTHOR'S SUMMARY.

THE EFFECT OF METHYLENE BLUE AND OTHER DYES UPON THE OXYGEN  
CONSUMPTION OF MAMMALIAN AND AVIAN ERYTHROCYTES. GEORGE A.  
HARROP, JR., and E. S. GUZMAN BARRON, *J. Exper. Med.* **48**:207, 1928.

The respiratory metabolism of non-nucleated mammalian erythrocytes is enormously accelerated and approaches the magnitude of the metabolism of the nucleated erythrocytes of birds on the addition of methylene blue (and certain other dyes), to a final concentration of from 0.005 to 0.0005 per cent. In the presence of methylene blue, the respiration is accelerated even when thousandth molar KCN is also present. The accelerated respiration due to methylene blue occurs at room temperature but it is most active at 38 C. Methylene blue in the foregoing concentration accelerates the respiration of avian (goose) erythrocytes to a much smaller extent than it does the respiration of the erythrocytes of mammalian blood, while the effect on anemic goose blood seems to be less than it is on cells of normal goose blood. Owing to a rather large initial carbon dioxide formation in defibrinated blood on incubation, which may not be related to the immediate respiratory process, proper respiratory quotients cannot be obtained in whole blood. When the cells are separated from the serum and suspended in Locke's solution, respiratory quotients are obtained on incubation comparable to those of other resting mammalian cells, as well as of the actively respiring erythrocytes of birds. The hypothesis is advanced that methylene blue acts in the rôle of an oxygen carrier, supplying a substance which has disappeared from adult mammalian non-nucleated erythrocytes and restoring their metabolic activity to an extent comparable to that of the young immature forms, or to that of the actively respiring avian (goose) blood.

AUTHORS' SUMMARY.

EXPERIMENTAL STUDY OF DIATHERMY. RONALD V. CHRISTIE, *J. Exper. Med.* **48**:235, 1928.

A method is described for measuring the relative impedance of living cells to diathermy currents. The diathermy current penetrates the living cell, and heat

production is intracellular as well as extracellular. A small proportion of the impedance of living cells to the diathermy current seems not to lead to the production of heat. Evidence is given that the addition of saponin produces an appreciable increase in the conductivity of an electrolyte. Its use is therefore contraindicated when electrical measurements are being made on biologic material. The currents used in diathermy behave as do high frequency currents of the pure sine wave form in respect to their passage through biologic material.

AUTHOR'S SUMMARY.

EFFECTS OF SPERM INJECTIONS INTO FEMALE RABBITS. W. T. POMMERENKE, *Physiol. Zool.* **1**:97, 1928.

Rabbits were given intravenous, intraperitoneal and intravaginal injections of rabbit spermatozoa and extracts of the testis. Others were given injections of rat spermatozoa. The serums and vaginal secretions of female rabbits which have received repeated intravenous or intraperitoneal injections of rabbit spermatozoa become highly toxic for rabbit spermatozoa. The life of spermatozoa normally deposited in the female genital tract of the rabbit is noticeably shortened by such previous injections of rabbit spermatozoa. Similar results were obtained when Ringer's solution extracts of fresh rabbit testes were repeatedly injected. There was no apparent effect on the estrous cycle, but injections given during pregnancy sometimes resulted in abortion or resorption of the fetuses.

Repeated injection of rabbit spermatozoa or of fresh testicular extracts into female rabbits may be followed by infertility lasting for from four to twenty-five weeks, and on return of fertility the number of young born in the first litters tend to be smaller than the earlier litter average. Control rabbits given corresponding injections of extracts of rabbit salivary glands and the ejaculated material coming from vasectomized male rabbits showed none of the foregoing results. Spermatoxins developed by means of rabbit spermatozoa are also toxic for rat spermatozoa, and vice versa. Repeated intravaginal injection of rabbit spermatozoa may induce antigenic effects in the blood and vaginal secretions of the experimental animals, but evidence of sterility is inconclusive.

THE TEMPERATURE OF NORMAL RABBITS. P. LAZARUS-BARLOW, *J. Path. & Bact.* **31**:517, 1928.

Except for a sudden increase in temperature after a cool period, or for a close thundery atmosphere, the temperature of a normal rabbit varies little with the external temperature. The temperature varies within rather wide limits and is subject to sudden rises for no apparent reason. Food causes a rise in temperature. A rise or fall from the mean of 2 F. is apparently significant. Sudden rises above 104 F. cannot be considered pathologic unless sustained.

THE CIRCULATION RATE IN SOME PATHOLOGICAL STATES, WITH OBSERVATIONS ON THE EFFECT OF DIGITALIS. J. G. KININMONTH, *Quart. J. Med.* **21**:277, 1928.

One hundred and sixty-three determinations of the circulation rate have been made by the ethyl iodide method on twenty-four patients suffering from various cardiac lesions, from anemia, from myxedema and from exophthalmic goiter. Aortic incompetence and early mitral stenosis do not directly affect the circulation rate. In a case of pulsus bigeminus resulting from digitalis, the bigeminal rhythm did not affect the cardiac output. In complete heart block, the output at each beat is large. In cardiac failure the circulation rate is low, this being due in ordinary types to a failure of the myocardium to maintain a sufficient output per beat with, in cases of auricular fibrillation, rapid irregular tachycardia a possible contributory factor. The circulation rate may be increased, decreased or unaffected by digitalis, different effects occurring in different patients and in the same patient at different times. An increase appears most likely to occur when

there are signs of cardiac insufficiency and a low circulation rate, but in such cases does not invariably occur. When signs of failure are absent or little marked and the circulation rate is not definitely low, an increase is less likely, the circulation rate usually remaining unaltered or decreasing. In cases of anemia, definite changes in circulation rate were not discovered. In exophthalmic goiter, the circulation rate tends to be high and in myxedema low.

N. ENZER.

AN INSULIN-RESISTANT DIABETIC. R. D. LAWRENCE, *Quart. J. Med.* **21**:359, 1928.

An unusual resistance to insulin was present in a young diabetic patient. In 1925, the patient's glycosuria was controlled by 40 units of insulin. A year later 100 units was necessary to maintain a normal blood sugar level, and six months later, on 220 units of insulin he excreted from 5 to 10 Gm. of sugar on a diet of carbohydrate, 60; protein, 80, and fat, 150. When insulin was omitted, coma supervened. The usual conditions encountered in diabetic patients resistant to insulin were absent in this case in which the blood sugar rose to extremely high levels after the injection of carbohydrate in spite of large doses of insulin. That this was not due to delayed insulin action or absorption was shown by the reduction of the blood sugar at a normal rate in the fasting condition. It would seem that there was a failure here of insulin to split up the injected carbohydrate. This failure to convert and store carbohydrate was shown by the spontaneous fall in the blood sugar when the patient was starved. Apparently, the insulin was able to control only the neoglucogenesis and ketogenesis from protein and fats. Possibly an enzyme other than insulin was lacking.

N. ENZER.

CREATINE AND RIGIDITY. M. HIRST and E. G. IMRIE, *Quart. J. Med.* **21**:401, 1928.

In parkinsonian rigidity, creatinuria occurs regularly. The amount of creatine excreted expressed as a fraction of the body weight seems to bear a direct relationship to the degree of rigidity.

N. ENZER.

CARBOHYDRATE AND FAT METABOLISM OF THE TISSUES. HANS-JOACHIM ARNDT, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:523, 1928.

By removal of small pieces of liver, muscle and other tissue at various times in the experiment, Arndt was able to trace changes in glycogen under conditions of fasting and the administration of insulin. Fasting was seen to cause glycogen to disappear from the liver in from one-half day to two days but was rapidly returned on large doses of sugar. While the fat of the body was practically free of glycogen, an overfeeding with sugar could cause comparatively large quantities of glycogen to appear in the fat cells of the fatty tissue. Though most of this disappeared when the animal was put back on a regular diet, the glycogen appeared to have been synthesized independently of the liver. The fat itself was not influenced by any of the foregoing substances or by the injection of insulin. Insulin, however, may cause a marked decrease in hypercholesteremia. The glycogen of the liver was greatly reduced when insulin was given in large and moderate sized doses but was increased when given in small doses with sugar. Insulin had been found to act through the placenta. It could act on the fetus whose blood sugar ran parallel with the mother's and the level was dependent on the doses of insulin. The depancreatized pregnant dog did not become hyperglycemic or show glycosuria. It seems that the fetal pancreas can secrete for the mother. There was no evidence in favor of the passage of insulin through the mammary gland. In rabbits, it was noted that continuous small doses of insulin had an intensifying action on the blood sugar and some animals progressed to a hypoglycemia. This was not noted in man. Insulin in man seemed to cause a glycogen formation in diabetes. When large doses of insulin and sugar were given, patients who had died of diabetic coma showed glycogen in the capillaries

and within blood vessels but not in the liver cells; but those diabetic patients who had died of intercurrent disease showed the usual glycogen in the liver.

JESSE LOUIS SERBY.

FAT METABOLISM FOLLOWING SPLENECTOMY. S. LEITES, *Klin. Wchnschr.* 7:1186, 1928.

After splenectomy, the splitting of the neutral fat by the liver is disturbed. Vicariously, the neutral fats are partially split in the lungs, and the oxidation of the lower fatty acids is delayed and disturbed (acetonemia).

E. F. HIRSCH.

THE PHARMACOLOGY AND PHYSIOLOGY OF IRON. E. STARKENSTEIN and H. WEDEN, *Klin. Wchnschr.* 7:1220, 1928.

The rapidity and completeness with which iron is deposited in the liver and spleen is an index of its pharmacologic, and probably also therapeutic, uselessness, as well as of its biologic function in the organism. Active iron circulates for a long time in the organism and is brought by the blood to all tissues, except the spleen.

The spleen absorbs primarily only the inactive ferric compounds, which are gradually liberated again. In the liver the iron is deposited only when it is reduced to an inactive form which probably is used in the building up of hemoglobin, but not for the biologic catalytic and pharmacologic iron activities in the organism.

E. F. HIRSCH.

THE RELATIONS BETWEEN THE PAROTID, THE PANCREAS, THE SUGAR OF THE BLOOD AND DIABETES MELLITUS. S. SEELIG, *Klin. Wchnschr.* 7:1228, 1928.

Ligation of the parotid duct was carried out in dogs to determine whether the effect of an internal secretion could be demonstrated. By this procedure the sugar concentration of the blood is maintained at a persistently low level. Dogs with pancreatic diabetes are not benefited by ligation of the parotid duct. If the duct is ligated before extirpation of the pancreas, the hyperglycemia is apparently not severe and the emaciation not so progressive. On the basis of results obtained in dogs, the parotid ducts of ten patients with diabetes mellitus were ligated. Of these, seven seemed to be influenced favorably and three apparently not.

AUTHOR'S SUMMARY.

DYE ADSORPTION BY THE SERUM OF PERSONS WITH LEAD POISONING. A. SEITZ, *Klin. Wchnschr.* 7:1234, 1928.

The adsorption power for dyes (naphthol yellow) of the serum of many patients with lead poisoning is diminished. In the absence of organic diseases, the results of such an adsorption test may be of value.

AUTHOR'S SUMMARY.

THE DIAGNOSIS OF PREGNANCY BY DEMONSTRATION IN THE URINE OF THE HORMONE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS. S. ASCHHEIM and B. ZONDEK, *Klin. Wchnschr.* 7:1404 and 1453, 1928.

The hormones of the ovary and of the anterior lobe of the hypophysis, produced in excess during pregnancy, are excreted in large quantities in the urine. The demonstration of ovarian hormone in the urine is not suitable as a biologic diagnostic test for pregnancy, because with functional disturbances of the ovary (climacteric, hyperhormone amenorrhea) large amounts of the hormone are excreted in the urine. The demonstration of the hormone of the anterior lobe of the hypophysis in small amounts of urine (from 1.2 to 2.4 cc.) according to a prescribed method is an excellent method for diagnosing pregnancy during the first months. The urine from 258 female (nonpregnant) and male patients was



tested for the presence of the hormone of the anterior lobe of the hypophysis. The hormone was found in four of these, an error in the diagnosis of pregnancy of 1.6 per cent. The urine of 197 pregnant women was tested in a similar way and of these 4, or 2 per cent, had no hormone content.

E. F. HIRSCH.

METABOLISM WITH CARDIAC DISEASE. D. LASZLO, *Klin. Wchnschr.* 7:1411, 1928.

There is a specific diminution of the phosphoric acid of the blood in uncompensated heart disease. During the period of improvement the phosphoric acid is retained, and the phosphoric acid added to the diet is also retained. The heart muscle and especially the skeletal muscle in those dying from heart disease have a diminished phosphoric acid content. The excretion of creatinine and uric acid is increased. In spite of the normal nonprotein nitrogen content of the blood with heart disease, creatinine and uric acid are increased. With muscular activity (work) in cardiac decompensation there is a marked increase of the lactic acid, uric acid and creatinine of the blood, while the inorganic phosphoric acid diminishes.

AUTHOR'S CONCLUSION.

THE ACTIVATION OF INSULIN IN ADULTS WITHOUT DIABETES. E. VOGT, *Klin. Wchnschr.* 7:1460, 1928.

Maximum activation of insulin is obtained by adding the serum of women obtained immediately before the onset of menstruation. Protein-free hormone of the follicles acts in the same way. In contrast, the serum of women after operative or roentgen-ray castration has little activating property. Activation occurs also by exposure to sunlight or to a carcinoma dose of roentgen-ray.

AUTHOR'S SUMMARY.

CHANGES IN THE K, CA AND CHOLIN CONTENT OF THE BLOOD IN ANGINA PECTORIS. D. DANIELOPOLU and M. MAXIM, *Klin. Wchnschr.* 7:1466, 1928.

There is a marked increase of the potassium and cholin during the anginal attack. These rapidly decrease within half an hour. Toward the end of the anginal attack, there is a slight increase of the calcium. Similar changes were observed in dogs with stimulation of the sinus caroticus.

AUTHORS' SUMMARY.

THE STOMACH AS A COREGULATOR OF THE ACID-BASE EQUILIBRIUM. M. BAKALTSCHUK, *Klin. Wchnschr.* 7:1551, 1928.

The increased acidity of the gastric secretion with inhalation of 3 and 5 per cent carbon dioxide should be regarded as a compensatory process caused by the acidosis. The stomach is important in regulating the acid-base equilibrium. The place where the stomach enters as regulator of the acid-base equilibrium is determined by the sufficiency of the important regulators, on the one hand, and the buffer capacity of the organism, on the other.

AUTHOR'S SUMMARY.

THE HYPOPHYSIS AND HYPOTHALAMUS IN EXPERIMENTAL DIABETES INSIPIDUS. P. TRENDELENBURG, *Klin. Wchnschr.* 7:1679, 1928.

After removal of the hypophysis, considerable amounts appear in the tuber cinereum of a substance which acts on the excretion of urine like the posterior lobe of the hypophysis and which is present only in traces in the tuber cinereum of normal animals. Diabetes insipidus may be hormonal in character, and when the production in the posterior lobe of a substance which inhibits urinary secretion ceases, then vicariously the tuber cinereum becomes active. Only after the destruction of this function is an irreparable diabetes insipidus established.

AUTHOR'S SUMMARY.

LACTIC ACID OF THE BLOOD IN DISEASE OF THE LIVER. H. SCHUMACHER, *Klin. Wchnschr.* 7:1733, 1928.

In severe forms of injury of the liver, the lactic acid content of the blood is increased, although in mild disease of the liver this may not be true. After intravenous injection of sodium lactate equivalent to 4 Gm. of lactic acid in 20 cc. of water, the lactic acid content of the blood in disease of the liver remains increased for a longer time than when the liver functions normally. Exceptions to this are observed in certain healthy persons.

E. F. HIRSCH.

ADMINISTRATION OF INSULIN THROUGH THE PORTAL SYSTEM IN DOGS. DAVID H. BOGGILD, *Acta path. et microbiol. Scandinav.* 5:118, 1928.

The experiments indicate that in dogs with a normal, or only slightly elevated, blood sugar level insulin has the same quantitative effect on the blood sugar when it is carried directly to the liver by way of the portal system as it has when introduced through the somatic peripheral circulation. Probably, however, parallel experiments should be made on dogs with hyperglycemia caused by pronounced diabetes, or from administration of dextrose, because experiments by Lewis and Magenta indicate that low blood sugar values after injection of insulin result in increased secretion of epinephrine.

AUTHOR'S SUMMARY.

### Pathologic Anatomy

COARCTATION OF THE AORTA OF THE ADULT TYPE. W. F. HAMILTON and M. E. ABBOTT, *Am. Heart J.* 3:381 and 574, 1928.

In the adult type of aortic coarctation a pathologic condition exists without counterpart in normal intra-uterine life. It consists of a sharp constriction amounting, in some cases, to a complete obliteration of the lumen of the descending aorta, adjacent to the insertion of the ductus arteriosus. At times, the constriction is so sudden and deep that the descending arch appears as if a ligature had been tied around it, and above and below this the aorta bulges outward in hour-glass fashion. Internally, the effect of the external strangulation in narrowing the lumen of the vessel is accentuated frequently by a fold or septum which stretches across that which remains of the aortic lumen, partially or completely closing it. The great vessels of the arch, especially the innominate and left subclavian arteries, are usually dilated, as are also the first three intercostals emerging below the stricture and the deep epigastric arteries, for it is by means of these vessels that the collateral circulation maintains life. Although the cause of coarctation is obscure, traction by the ligamentum arteriosum increases the kinking of the descending arch and at times produces a tent-shaped aneurysm of the aorta with its apex toward the ligamentum. Loriga believes the condition begins in the primitive left aorta, which unites the left fourth (aortic) arch with the fifth and sixth arches of this side.

A reproduction of a table illustrates the sex and age incidence in 200 cases.

Age in Decades	Males	Females	Sex Unknown	Totals
3 to 10 years.....	6	3	..	9
10 to 20 years.....	34	11	..	45
20 to 30 years.....	34	13	2	49
30 to 40 years.....	34	8	3	45
40 to 50 years.....	21	7	..	28
50 to 60 years.....	9	3	..	12
60 to 70 years.....	7	3	..	10
70 to 92 years.....	2	..	..	2
	147	48	5	200

The degree of stenosis was: moderate in 45 bodies, and the aperture allowed the passage of the little finger; extreme in 108, and admitted objects from a bristle to 6 mm. in diameter, and complete in the remaining 47. Minor cardiac anomalies were present frequently in the form of bicuspid aortic valves, anomalous origins of the arteries from the arch, persistent superior vena cava of the left side and defects of the interauricular and interventricular septums. In the body at large, there were additional anomalies, as hypospadias, absence of the left kidney, ureter and seminal vesicle, diaphragmatic hernia and subluxation of the joints. The causes of death were: spontaneous rupture of the heart and ascending aorta in 35 cases; rupture at the coarctation in 5; aneurysm, saccular or dissecting, in 39; mycotic endocarditis in 14, 4 of which were due to *Streptococcus viridans*; cerebral lesions in 26, of which 1 was due to embolism, the rest to hemorrhage; decompensation in 60, sudden heart failure in 17 and other causes in 36. The case report presented concerns a boy, aged 14, who for four years had had dyspnea, precordial pain, weakness and cyanotic clubbed fingers. The radial pulse was typically collapsing while the femoral and tibial pulsations were impalpable. There was a rough systolic heart murmur, with a blood pressure of 150 systolic and 50 diastolic. Death followed a hemiplegia, which rendered the right arm and leg powerless. Autopsy was confined to the trunk. There was a coarctation of the aorta at the site of the ligamentum arteriosum, and the vessel wall on either side of this presented a smooth, shining biconcave surface suggesting an anomalous development from the primitive aortic arch at its junction with the left sixth arch. In addition, there were a bicuspid aortic valve, subaortic stenosis and an anomalous vessel from the descending arch.

GEORGE RUKSTINAT.

TISSUE CHANGES IN PARATHYROID TETANY AND IN GUANIDINE POISONING.

L. A. ELKOURIE and E. LARSON, Am. J. Physiol. **87**:124, 1928.

When the changes induced by parathyroid tetany and those induced by guanidine intoxication in dogs were compared, the two conditions were found to have very different clinical syndromes; the visceral congestion of parathyroid tetany was lacking in guanidine poisoning, and the hepatic fatty degeneration of the latter was absent in the former. Necrosis of the liver was present in both.

H. E. EGGERS.

NECROPSY FINDINGS UNDER CRACKED-POT TYMPANY. JOSEPH WALSH, Am. Rev. Tuberc. **18**:202, 1928.

From a necropsy study of eleven cases it would appear that, when cracked-pot tympany occurs in tuberculosis of the lungs apart from pleural effusion, the diagnosis of superimposed cavities was practically assured. The single exception found in these cases was associated with a rare condition in which a combination of cavity and central consolidations existed, so that a blending of superimposed tympany was produced.

H. J. CORPER.

THE RELATIVE INCIDENCE OF CALCIFIED LESIONS IN THE TRACHEOBRONCHIAL, CERVICAL AND ABDOMINAL LYMPH NODES. F. H. FRASER, Am. Rev. Tuberc. **18**:336, 1928.

Roentgen examination was made of 151 children, including 31 with tracheo-bronchial lesions, in order to determine whether there were calcified lymph nodes in the neck and abdomen. Two cases with cervical calcium were found; four had cervical tuberculosis without demonstrable calcium. Abdominal calcified nodes were present in two cases without signs or symptoms. All roentgenographically positive patients reacted positively to tuberculin and were without pulmonary lesions.

H. J. CORPER.

THE INCIDENCE OF ROENTGENOGRAPHICALLY OBSERVED CALCIFIED PULMONARY FOCI AND THEIR SIGNIFICANCE. JOHN T. FARRELL, JR., *Am. Rev. Tuberc.* 18:344, 1928.

Of 1,034 adult patients whose chests were examined by the roentgen ray, 801, or 77.46 per cent, presented evidence of a primary "Affekt" or of a calcified reinfection. Of this group, 750, or 72.93 per cent, presented primary "Affekt." The lower portion of the right lung, the best aerated portion, exhibited the highest incidence of calcified foci. There was a slightly higher incidence of primary foci of the lung in the male patients. In those without roentgen evidence of apical tuberculosis of the adult type, there was a higher incidence of calcification than in those with clinical tuberculosis. No relationship as to age was established in this group of patients, whose ages ranged from 15 to 84 years. With advancing age, there was an increase in the proportion of patients who showed the more extensive degrees of calcification.

H. J. CORPER.

THE DISTRIBUTION OF VALVES AND THE FIRST APPEARANCE OF DEFINITE DIRECTION IN THE DRAINAGE OF LYMPH IN THE HUMAN LUNG. OTTO F. KAMPMEIER, *Am. Rev. Tuberc.* 18:360, 1928.

Lymph vessels begin to invade the lung in human fetuses of 2 months. At the end of the third month, not only have they traversed the entire organ by extending along the bronchi, pulmonary arteries and veins, but they are creating a subpleural network. Developing valves, already present in the lymphatics of the jugulosubclavian territory at the end of the second month of prenatal life, arise in the lymphatic plexus of the mediastinum shortly afterward, and in that of the hilum of the lung not more than a month later. Despite the fact that the lung does not perform its functions until birth, it in nowise lags behind any other part of the body in the prompt construction of its lymphatic organization. Its valves become exceedingly numerous in the period from the third to the fourth months. The mode of valvulogenesis in the pulmonary lymphatics conforms to that in the peripheral lymphatic plexuses elsewhere in the body. A valve originates either by the tangential ingrowth of one lymph vessel into another during the formation of the plexus, or from intimal flanges proliferated at the mouth of confluences established earlier. The valves of the deep lymphatics in the hilum of the lung point toward the mediastinum, and consequently send the lymph stream in that direction. In the channels connecting the deep pulmonary lymphatics and the peripheral or subpleural plexus, most valves point outward, that is, toward the pleura; however, a few instances occur, especially at the margins of the lobes, in which they are turned in the reverse direction. In the material examined for the arrangement of the lymphatic valves in the lung (in fetuses from the middle of intra-uterine life, and in a new-born infant who had breathed), these structures were found in great numbers in the subpleural plexus on the medial face of the lung next to the heart, in moderate abundance on the diaphragmatic surface and on the costal surface near its ventral border, but were absent on the dorsal side and at the apex. This distribution represents a striking demonstration of the purpose of the valves as regulators of the lymph drainage when it tends to be disturbed or impeded by a compressive force on it externally, as by muscular action. It was further observed that the channels of the lymphatic plexus which bore numerous valves, particularly those on the medial or cardiac side of the lung, are larger and more voluminous than the valveless ones on the dorsal side. The distinctions described in the lymphatic volume and valvular distribution, signifying differences in the underlying hydrostatic conditions, suggest a possible relationship with the diversity in the course of the tuberculous process, for example, in the different parts of the lung.

H. J. CORPER.

MILIARY TUBERCULOSIS IN CHILDHOOD. JOSEPH GREENGARD, *Am. Rev. Tuberc.* 18:392, 1928.

Fifty-four cases of miliary tuberculosis in childhood are reviewed clinically, and complete observations at autopsy are discussed in thirty-five of these. Tuber-



culous meningitis occurred in 80 per cent of the cases in which autopsy had been performed. Caseation of the tracheobronchial lymph nodes was universally present in the series in which autopsies were performed. Caseous lesions within the lung tissue, which appeared to represent the primary nidus of infection, were noted in twenty-four cases, and pulmonary cavitation was seen in five. Caseation of mesenteric lymph nodes was present in twenty-four cases, and was unaccompanied by advanced tuberculosis of the gastro-intestinal tract in most instances. The occurrence of suppurative otitis media as a concomitant lesion in these cases was noted.

H. J. CORPER.

INCIDENCE OF PLEURAL LESIONS AS SHOWN BY ROENTGENOGRAPHS IN CHILDREN KNOWN TO BE TUBERCULOUS. LLOYD B. DICKEY and L. H. GARLAND, *Am. Rev. Tuberc.* **18:404**, 1928.

In a series of roentgenograms of the chests of 327 children known to be tuberculous, and in a control series of 50, a surprisingly high incidence of pleural lesions can be demonstrated. A high incidence is shown in the larger positive series for the 1 to 2 year age group, the age at which the evidence of tuberculous pleurisy, at least, is considered to be rare. Fifty-eight per cent of patients examined at this age showed pleural lesions roentgenologically. No relation could be shown between pleural lesions and the enlargement of hilum lymph nodes. Pleural lesions in children who reacted positively to tuberculin tests were no more common than in those who reacted negatively.

H. J. CORPER.

BRONCHOLITHIASIS. BARNET P. STIVELMAN, *Am. Rev. Tuberc.* **18:430**, 1928.

A patient is reported who engaged in an occupation which was the direct cause of his silicotic process of the lungs. As is a common occurrence in such cases, this patient developed phthisis. No light was shed on the etiology of the multiple lung-stone formation, although it is possible that the irritating silica-dust particles, in addition to calling forth their distinctive reaction, also formed the nuclei of future calculi. Definite bronchial colic accompanied the expulsion of the lung-stones, and it is fair to assume that one of these attacks of forced expiratory dyspnea was the cause of the rupture of the lung of the left side at a point already weakened by a tuberculous process or a subpleural emphysematous bleb.

H. J. CORPER.

CHANGES IN THE BRAIN IN INCREASED INTRACRANIAL PRESSURE. GEORGE B. HASSIN, *Arch. Neurol. & Psychiat.* **20:1172**, 1928.

Increased intracranial pressure produces typical histologic changes in the brain. The changes are degenerative, associated with reactive glia phenomena and are analogous to the changes that result from prolonged pressure (by a tumor) on the brain or spinal cord. In the corpus callosum, optic nerve, chiasm and optic tract, the changes are diffuse and noticeable; in the ganglion cells, they are mild. The degenerative changes are combined with areas of rarefaction which are due to stasis of tissue fluids and accumulation, in some instances, of catabolic products, such as basophil-metachromatic substances, lipoids and methyl blue granules. The extent of the changes varies according to the intensity and the duration of the increased pressure. The histologic changes in pressure are of mechanical origin and are due, as in the corpus callosum, to the actual tearing of nerve fibers or to nutritional disturbances brought on in some parts of the brain by stasis of the tissue fluids. The subarachnoid space and the blood vessels usually exhibit proliferative reactive phenomena. When due to tumors, the changes produced by increased intracranial pressure are more marked in extracranial than in intracerebral types of tumor.

AUTHOR'S SUMMARY.

PROGRESSIVE DEGENERATIVE SUBCORTICAL ENCEPHALOPATHY (SCHILDER'S DISEASE). JOSEPH H. GLOBUS and ISRAEL STRAUSS, Arch. Neurol. & Psychiat. 20:1190, 1928

Progressive degenerative subcortical encephalopathy is the name suggested for a demyelinating and sclerosing process in the brain of young children involving the white matter without involvement of the gray matter of the cerebral and cerebellar hemispheres. The disease may be due to some toxic factor, of unknown nature, which affects the normal growth of the parenchymatous structures in the subcortical regions of the brain, causes their dissolution and results in proliferative glial changes. Clinically, it is characterized by a rather abrupt onset of illness, which often takes the character of a gastro-intestinal disturbance, and which, after a short period of apparent recovery, is followed by a series of generalized cerebral manifestations. Among the latter, mental dilapidation, spastic paralysis accompanied by advancing rigidity, contractures and convulsive seizures appear in varying sequence. Advancing blindness with or without optic atrophy, deafness and aphasia may develop at any stage of the illness, though most frequently early in the clinical course. Some of the conditions described as chronic encephalomyelomalacia, diffuse sclerosis, perivascular myelin necrosis, encephalitis periaxialis diffusa, sclerosing encephaloleukopathia and interlobar symmetrical sclerosis should be grouped under the general name of progressive degenerative subcortical encephalopathy.

AUTHORS' SUMMARY.

THE BRAIN IN MONGOLIAN IDIOCY. LEO M. DAVIDOFF, Arch. Neurol. & Psychiat. 20:1229, 1928.

The brain in mongolian idiocy shows: agenesis, as evidenced by cell poverty and failure of gyral development (there probably is also a degenerative process in very early life, increasing the paucity of the ganglion cells in the cerebral cortex); aplasia, as shown by its small size in comparison with that of children of corresponding age and paragenesis, as demonstrated by the frequent occurrence of anomalies.

AUTHOR'S SUMMARY.

PERSISTENT THYMUS IN EXOPHTHALMIC GOITER. E. B. POTTER, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A. S. WARTHIN, Ann Arbor, George Wahr, 1927, pp. 205-220.

Among the records of 2,300 autopsies in the pathologic laboratory of the University of Michigan, Potter found twenty-two proved cases of exophthalmic goiter. In nineteen cases, death was said to be due to thyrotoxicosis, in the remaining three cases pneumonia was the stated cause of death. Hyperplasia of the thymus, as well as generalized lymphoid hyperplasia, was found in every case. These individuals belong to a distinct diathesis, the so-called "Graves' constitution (Warthin)."

WALTER M. SIMPSON.

SIGNIFICANCE OF KIDNEY INFILTRATIONS IN THE GROSS PATHOLOGICAL DIAGNOSIS OF LYMPHOBLASTOMA. C. H. FORTUNE, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A. S. WARTHIN, Ann Arbor, George Wahr, 1927, pp. 221-231.

Fortune lays emphasis on the value of grossly visible lymphoblastomatous infiltrations of the kidney in differentiating lymphoblastoma from Hodgkin's disease, generalized lymphoid hyperplasia due to infection or metastatic carcinoma. Lymphoblastomatous infiltrations of the liver occur with almost equal frequency, but the renal changes are more easily recognized on gross inspection. Most characteristic is the focal type, in which the lesions are usually cortical and are seen as circumscribed, whitish, firm areas when the fibrous capsule is stripped back. In some cases, the infiltrations are more diffuse, resembling the "large white kidney" of

nephritis. On section, there are often found pale, firm streaks in the labyrinthine areas, running radially and more or less clearly differentiated from the surrounding kidney substance.

WALTER M. SIMPSON.

ABERRANT PANCREATIC TISSUE; AN ANALYSIS OF 150 HUMAN CASES WITH A NEW CASE. WALTER M. SIMPSON, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A. S. WARTHIN, Ann Arbor, George Wahr, 1927, pp. 435-459.

Simpson reviews the world's literature concerned with aberrant pancreatic tissue, and summarizes 150 cases in tabular form. An additional case of pancreas accessorium associated with aberrant Brunner's glands in the stomach wall, mistaken clinically for carcinoma, is recorded. The mucosa overlying the pancreatic tissue was intact and showed a distinct central funnel-like umbilication, lined by typical duodenal mucosa, toward which the large excretory ducts converged. The pancreatic lobules were most abundant in the subserosa, while the ducts were found in large numbers in the muscularis, simulating the microscopic picture of adenomyoma or infiltrating adenocarcinoma. Many islands of Langerhans were found lying free in the muscularis, widely separated from the pancreatic acini. In the ducts was a finely granular albuminoid precipitate, similar to that seen in the pancreatic ducts proper, giving probable evidence of functional activity. The developmental genesis of these misplaced nodules is discussed in detail, together with a discussion of the frequent association of accessory pancreatic tissue with diverticula of the stomach, duodenum, jejunum or ileum. Emphasis is placed on the growing interest in aberrant pancreatic tissue because of the frequency with which they are mistaken, clinically and roentgenologically, for neoplastic growths.

AUTHOR'S ABSTRACT.

EXPERIMENTAL EDEMA AS AN AID TO HISTOPATHOLOGIC STUDIES. S. R. HAYTHORN, CONTRIBUTIONS TO MEDICAL SCIENCE DEDICATED TO A. S. WARTHIN, Ann Arbor, George Wahr, 1927, pp. 491-501.

Edema, when produced artificially in connection with specific experimental lesions, may serve as an aid in studying the cells taking part in the reactions under investigation. Its mode of action is that of flushing the tissues with fluid and relieving the pressure of surrounding elements so that the cells become separated and may then be subjected to individual examination. It is especially useful when used together with special technical methods designed to bring out cell characteristics.

Haythorn found the procedure useful in studies on anthracosis, the identification of pigment phagocytes, the histogenesis of the tubercle and on the origin of the Langhans giant cell. The author is of the opinion that the method probably possesses a wide field of application.

WALTER M. SIMPSON.

INVASION OF THE SKULL BY DURAL TUMORS. J. TAYLOR, Brit. J. Surg. 16:6, 1928.

One may regard the dural tumors as growths of slow spread, local malignancy and occasional metastasis. Their powers of malignant infiltration are seen in their invasion of the coverings of the brain, but only in rare instances do they cross the arachnoid spaces to penetrate the brain itself. This last character of failure to cross the arachnoid they share with growths arising in the brain, which do not commonly invade the dura. They are exactly paralleled in both their main varieties by the periosteal sarcomas of the long bones, the difference between the dural and periosteal growths being found in the degree rather than in the fact of malignancy in the latter. The observations given in this communication certainly in no way indicate the arachnoid as the source of origin of these tumors; nor, it should be pointed out, do they deny such a possibility, because it

has been shown that malignant growths of divers characters may result in identical bony changes, provided they invade the appropriate layers of the bone and periosteum. These observations, however, undoubtedly show that the normal proliferation of the arachnoid into the substance of the dura has no special and unique influence on the form of the growth. They further suggest that the form and spread of the tumors are related to the function of the dura as a periosteum rather than as a covering for the brain. In the presence of the exhaustive labors that have been devoted toward the determination of the tissues from which the dural tumors arise, the writer does not feel qualified to express his opinion on this subject. He rather wishes to emphasize that the facts of their form and growth are those here described; that if these are critically examined, the dural tumors, whatever their origin, take their place naturally among the more commonplace pathologic processes. Thus the attribution to them of characters special and unique is warranted neither by clinical nor by pathologic facts.

## AUTHOR'S SUMMARY.

URETHRAL DIVERTICULA. T. B. MOUAT, Brit. J. Surg. 16:51, 1928.

Urethral diverticula may be congenital or acquired, and the causes of the acquired variety vary in the different portions of the canal. In the prostatic urethra, pouches of this kind are most commonly acquired from the gradual increase in size, and communication with the urethra, of a sac or sacs containing calculi which formed in the gland substance. In a second and less common variety of acquired diverticulum, the prostatic urethra may gradually become distended to form a smooth walled sac as the result of a lodgment of a stone or stones in that portion of the canal. As rarer causes of prostatic pouches, it has been suggested that cysts or abscesses of the gland substance might burst into the urethra and persist as acquired diverticula communicating with the canal. In the anterior urethra acquired diverticula are much more common. The causes are principally trauma of various kinds and periurethral abscesses. Illustrated cases are presented. Regarding the composition of urethral and para-urethral stones, it is agreed that stones formed in the prostatic substance are composed of calcium phosphate, calcium carbonate and organic material, and that any of the ordinary kinds of calculi may descend the urinary tract to lodge secondarily in the urethra. The composition of stones found primarily in urethral diverticula is under considerable discussion, as some writers state that such stones must necessarily be wholly of phosphates, whereas others do not see any difficulty in assuming that other than phosphatic calculi may be found in situ.

NATHAN N. CROHN.

DIVERTICULOSIS OF THE APPENDIX AND PSEUDOMYXOMA PERITONEI. A. J. GARDHAM, C. C. CHOYCE and M. RANDALL, Brit. J. Surg. 16:62, 1928.

The case reported is that of a diverticulum, the size of a pea, attached to the antimesenteric border of the appendix. Microscopically, the diverticulum protrudes through a cleancut gap in the muscularis, and consists of a single layer of mucous membrane with a covering of granulation tissue, a little fibrous tissue and a few muscle fibers. Gardham notes from the literature that diverticula of the appendix frequently appear to lead to pseudomyxoma of the peritoneum. The diverticulum is found as a result of the destruction of a small area of the muscle coat of the appendix by interstitial abscesses during an attack of appendicitis. When the condition subsides without involvement of the mucous membrane, a diverticulum results. If the diverticulum perforates in cases in which the inflammation subsides without leading to abscess formation, pseudomyxoma peritonei ultimately develop. A case of pseudomyxomatous cyst of the peritoneum following appendicitis is reported. The cyst filled the whole space from the ascending to the descending colon laterally, and from the transverse colon to near the brim of the pelvis below. The perforated tip of the appendix extended into the cyst. The secretion of mucoïd material, when the peritoneum becomes involved, persists even after removal of the appendiceal or ovarian cyst.

NATHAN N. CROHN.



STAPHYLOCOCCAL SUPPURATIVE NEPHRITIS (CARBUNCLE OF THE KIDNEY).  
B. M. DICK, Brit. J. Surg. **16**:106, 1928.

A review of the literature shows only twenty-seven cases reported. The author adds three cases. The chief characters of the lesion are an acute or subacute hematogenous infection of the parenchyma of one kidney by *Staphylococcus aureus*, the onset of which is frequently preceded by some trauma to the organ. The source of origin is most often a skin lesion, such as a whitlow, boil or carbuncle. The appearance of the kidney varies according to the stage of involvement; the most constant observation is that of multiple areas of necrosis or suppuration confined to one area of the substance of the kidney. Fusion of the suppurative foci gives rise to a honeycomb-like necrotic cavity or a circumscribed encapsulated abscess and a localized enlargement of the affected area. A perinephritic abscess may result, but rupture into the renal pelvis is unusual. Only in one recorded case was the infection bilateral.

NATHAN N. CROHN.

CALCIFICATION OF THE GALLBLADDER. J. J. ROBB, Brit. J. Surg. **16**:114, 1928.

Calcification of the gallbladder is accompanied in 90 per cent of cases by gallstones. The author describes his specimen to be about the shape and size of a large walnut. The serosa was fibrotic, and could be stripped cleanly from the subjacent bony-like layer, the latter averaging 0.2 cm. in thickness. The mucosa was absent and was replaced by a layer of lime salts. The author emphasizes the fact that the calcification of the wall was confined entirely to the parts surrounding the calculi and did not extend into the cystic duct. The causal relationship consists in the constant trauma of the muscular wall over the unyielding calculi. This trauma is productive of degenerative changes. Bacterial infection plays an insignificant part in this type. In the infective type which may be unassociated with gallstones, calcification may be the termination of chronic cholecystitis. The process of calcification is differentiated from the deposition of calcium on the mucosa.

NATHAN N. CROHN.

ENCEPHALO-MYELITIS IN VIRUS DISEASES AND EXANTHEMATA. H. M. TURNBULL, Brit. M. J. **2**:331, 1928.

Focal histologic changes extend from the cortex of the brain to the lumbosacral cord in postvaccinal encephalitis. Acute changes noted in persons dying from fourteen to seventeen days after vaccination consist of slight intermittent infiltrations of the leptomeninges, chiefly about the veins, with small and large lymphocytes, plasmacytoid and true plasma cells, large mononuclear leukocytes and endothelial cells. The essential change consists of perivascular and marginal zones of demyelination which form wide sleeves, especially about the veins, and extend along their branches. In the subacute type, the adventitial sheaths are distended with a mosaic of large fat granule cells. Turnbull suggests calling the condition disseminated encephalomyelitis of the postvaccinal type, since it differs from poliomyelitis and lethargic encephalitis and belongs in a group characterized by demyelination as the disseminated myelitis of Westphal and disseminated sclerosis.

GEORGE RUKSTINAT.

ENCEPHALO-MYELITIS IN VIRUS INFECTIONS. J. McINTOSH, Brit. M. J. **2**:334, 1928.

Two theories are advanced to explain the occurrence of postvaccinal encephalitis: first, that the disease is vaccinal in origin, and second, that it is due to the presence of dormant virus stimulated into activity by vaccination, which virus may be that of poliomyelitis, lethargic encephalitis, herpes febrilis or some unknown virus. The arguments McIntosh uses to support the first theory are as follows: Intracerebral inoculations of neurotropic strains of variolous lymph produce an encephalitis in rabbits presenting the main histologic characters of postvaccinal

encephalitis. Intravenous injections of neurotropic strains of vaccinia produce focal lesions in the internal organs similar to those found at times in cases of postvaccinal encephalitis and in variola. He reports the failure to produce any of the known virus infections of the central nervous system by animal inoculation with material from postvaccinal encephalitis. The occurrence of a similar cerebral lesion is reported in a case of encephalitis following smallpox.

GEORGE RUKSTINAT.

**PAINFUL CALCIFIED AND OSSIFIED VAGINAL CORPUSCLES.** R. NOEL and C. PELLANDA, *Lyon Chir.* **25**:452, 1928.

The authors find that calcified and ossified vaginal corpuscles are frequent, having observed them 100 times in three years. Usually, symptomless and discovered only accidentally, they are occasionally painful and cause dyspareunia. The largest and most painful ones are found in patients with ovarian disturbances due to postpuerperal ovaritis or to genital aplasia following hysterectomy without conservation of the adnexa. Local infection is of no importance in their production. The location is remarkably constant, and it is definitely lateral at the junction of the upper and middle thirds of the vagina. The vaginal wall moves freely over them, and they can be easily removed through a small incision. They are usually single, but there may be two or three; in the latter case, one is always larger than the other two. The size never exceeds that of a small pea, and is usually much smaller. The form is regular, round or slightly elongated, and the consistency is hard. The microscopic appearance is constant: a vascular fibrous capsule surrounding concentric lamellae of calcified material. This material shows the characteristics of bony tissue, with osteoblasts, bone marrow containing blood capillaries, and lymphocyte and plasma cell elements. The bodies resemble Pacini's corpuscles and probably originate in degeneration of these sensory organs. There may be some significance in the relation between the calcareous degeneration of the sensory end-organs and the attenuation of ovarian function frequently found to be associated with the process.

BEATRICE R. LOVETT.

**XANTHOCHROMIA OF CEREBROSPINAL FLUID IN INFANTS.** J. P. GARRAHAN, *Rev. franç. de pédiat.* **4**:483, 1928.

From the study of 196 specimens of cerebrospinal fluid from 135 new-born infants, Garrahan concludes that xanthochromia of the cerebrospinal fluid is physiologic in the new-born infant. Only 20 of 177 specimens of cerebrospinal fluid from infants ranging in age from 1 to 10 days were colorless. The intensity of the yellow coloration increases, as a rule, during the first few days and begins to diminish in the second week. The presence of even large numbers of erythrocytes in the cerebrospinal fluid of new-born infants is normal. The effect of birth trauma on the production of xanthochromia is not clear. The yellow color of the cerebrospinal fluid of new-born infants appears to be due to bilirubin. Van den Bergh's indirect test almost always gives a positive result, and all new-born infants with icterus have a yellow cerebrospinal fluid. Little is known concerning the genesis of the xanthochromia of the cerebrospinal fluid of new-born infants. It is not pathognomonic of meningeal hemorrhage.

**CHANGES IN THE VAGINAL EPITHELIUM DURING MENSTRUATION AND PREGNANCY.** KARL ADLER, *Arch. f. Gynäk.* **134**:505, 1928.

The vaginal epithelium is shown to undergo cyclic changes during the child-bearing age analogous to changes occurring in the endometrium. The material was divided into three series: that obtained from women in the child-bearing age; during pregnancy—post partum and puerperium—and a control series from prepuberty and climacteric patients. The cyclic changes were dependent solely on the ovarian function. The upper zone of the stratified epithelium formed a differentiated layer which was the forerunner of a still more differentiated layer

of flat cornified cells. The latter layer reached the height of formation during the premenstrual phase, but was absent immediately after menstruation. This layer is termed "functionalis." The cyclic functions were present in patients in whom only the uterus was removed. During pregnancy the zona functionalis was especially well developed by the second month, and was considered diagnostic. Immediately after the delivery, this layer was found to be traumatized and partially removed, but during puerperium, when the ovarian function was held in abeyance and lactation amenorrhea was present, the "functionalis" layer was entirely absent. During childhood and climacterium this layer was likewise absent. The author considered the ovarian hormone the basis for these changes.

A. J. KOBAK.

FOREIGN BODY IN ABDOMEN. J. J. GENKIN, Arch. f. klin. Chir. **151**:646, 1928.

Following operation for cystic ovary, a movable swelling developed in the abdomen, which proved to be a chylous cyst of the mesentery containing a gauze tampon rolled into a ball.

CEREBRAL HEMORRHAGE IN YOUNG PERSONS. OTTO MARBURG, Deutsche Ztschr. f. Nervenhe. **105**:22, 1928.

Four cases of cerebral hemorrhage in relatively young persons are reported with no evidence post mortem of either cardiac disease or gross vascular changes. The process was not one of diapedesis, as actual rupture of the vessel wall was seen. Three patients suffered from griplike infection shortly before the hemorrhage, and Marburg found proliferation and swelling of the capillary and arteriolar endothelium. He concludes that obstruction of the capillary bed resulted in an increased vascular pressure and rupture of a vessel. Only one patient seemed to have abnormally thin vessel walls.

ROY GRINKER.

THE PATHOGENESIS OF MULTIPLE SCLEROSIS. H. PETTE, Deutsche Ztschr. f. Nervenhe. **105**:77, 1928.

Two acute cases of disseminated encephalomyelitis and one of multiple sclerosis were studied clinically and anatomically. It is concluded that both belonged to the same disease entity, which is caused by some specific neurotropic virus. This conclusion is based on the presence of inflammatory reactions in the cords of both groups.

ROY GRINKER.

### Pathologic Chemistry

CHEMICAL ANALYSIS OF BLOOD IN PATIENTS WITH SENILE CATARACT. C. S. O'BRIEN and V. C. MEYERS, Arch. Int. Med. **42**:376, 1928.

In fifty-four patients with cataract, chemical examination of the blood gave essentially negative results, except for an increase of cholesterol in 54 per cent of the cases.

HAMILTON R. FISHBACK.

THE PLASMA CHLORIDES IN OBSTRUCTIVE JAUNDICE. I. S. RAVDIN and M. E. MORRISON, Arch. Int. Med. **42**:491, 1928.

There is a constant depression of the plasma chloride value after ligation of the common bile duct and cholecystectomy. After either cholecystectomy or ligation of the bile duct alone depression of the plasma chlorides was not found.

HAMILTON R. FISHBACK.

THE ESTIMATION OF SILICA IN TISSUES. E. J. KING, J. Biol. Chem. **80**:25, 1928.

A colorimetric method is described whereby the minute amounts of silica present in animal tissues may be approximated with considerable accuracy. A tabulation is presented, indicating the concentrations of silica ordinarily found

in the lungs, livers and kidneys of healthy dogs and rabbits. The normal silica content of lung tissue of the human being would appear to be about 0.02 per cent, becoming increased to values exceeding 1.8 per cent during silicosis.

ARTHUR LOCKE.

THE EFFECT OF AGE ON THE TOTAL AND COMBINED CHOLESTEROL OF THE BLOOD SERUM. R. E. SHOPE, *J. Biol. Chem.* **80**:141, 1928.

THE HYPERCHOLESTEROLEMIA OF FASTING AS INFLUENCED BY THE SEPARATE ADMINISTRATION OF FATS, CARBOHYDRATES, AND PROTEINS. *Ibid.* p. 133.

CHOLESTEROL ESTERASE IN ANIMAL TISSUES. *Ibid.* p. 127.

The blood contains, at birth, little cholesterol and no cholesterol ester. The ester first appears, in quantity, after the ingestion of colostrum and the commencement of the nursing period. During this period, the total cholesterol concentration rises rapidly, reaches an early maximum and then declines gradually with the approach of maturity. The decline is more uniform and regular in the male than in the female.

Cholesterol does not appear to have any established function in the process of fat metabolism. The cholesterol content of the blood is not notably increased after maintenance of 48 hours on a diet consisting exclusively of fat, nor is the hypercholesterolemia of fasting animals affected differently by feedings of fat than by feedings of carbohydrate and protein.

The cholesterol ester content of the blood decreases rapidly after death because of the uncompensated activity of the hydrolytic enzyme, cholesterol esterase.

ARTHUR LOCKE.

STUDIES ON THE COMPOSITION OF HUMAN MILK. M. BELL, *J. Biol. Chem.* **80**:239, 1928.

Consecutive analyses of the breast milk of eighty-eight normal women are reported. The tables presented indicate that the ash and protein content of the milk steadily decreases during the first few days post partum, while the fat and lactose content gradually increases. The influence of supplementary feedings of carbohydrate and fat on the composition and volume of the milk is discussed.

ARTHUR LOCKE.

TOTAL SUGAR OF BLOOD AND URINE. THE HYDROLYZABLE SUGAR OF BLOOD. M. EVERETT and F. SHEPPARD, *J. Biol. Chem.* **80**:255, 1928.

Leukemic blood contains more hydrolyzable sugar than normal blood, but not enough more to indicate the white cells as its chief source. The sugar is actually present and is not an analytical artefact. It resembles, but may not be identical with, glycogen. (The possible derivation of the sugar from the minute concentration of glycoprotein known to be present in the blood appears not to have been considered.)

ARTHUR LOCKE.

OSMOTIC PRESSURE OF BLOOD PROTEINS IN NEPHRITIS. C. L. COPE, *Quart. J. Med.* **22**:91, 1928.

The technic of Verney has been employed by Cope to determine the cases of osmotic pressure of the blood plasma proteins in nephritis. In nonedematous nephritis the protein osmotic pressure is unreduced, except slightly just before death; it may, however, be higher than normal, though this rise is not necessarily associated with high blood pressure. In cases of nephritis with edema, a definite fall in protein osmotic pressure occurs, and this disappears coincidentally with the subsidence of the edema. In cardiac failure, the protein osmotic pressure may be undiminished when edema is present, or may be found markedly lowered in the absence of demonstrable edema.



CREATINURIA AFTER FRACTURES. M. HIRST and C. G. IMRIE, *Quart. J. Med.* **22**:153, 1928.

Hirst and Imrie assert that creatinuria occurs after fracture of bones. The amount of creatine found to be excreted in twenty-four hours in different cases has varied from traces to more than 500 mg. It disappears gradually from the urine as healing takes place and the patient is up and about. The hourly rate of excretion is lowest at night. This creatinuria has been observed in four cases of fractured femurs (all that were studied); in some fractures of the tibia and fibula; in a case of fractures of the pelvis, and in a less degree in several, though not all, cases of fracture of the tibia alone. Administration of thyroid gland increased the output of creatine threefold in a case of fracture of the femur. The hourly rate of excretion was increased during each of the four periods into which the twenty-four were divided; this increase was most marked at night, when, without thyroid, the output was smallest; at other times of the day it was such that the maximum output was shifted from the morning to the evening so as to coincide with the maximum nitrogen output. The increase in the output of creatine preceded any change in the basal metabolism or in the other nitrogenous constituents of the urine. Creatine was not increased, and the uric acid showed only a slight rise. A diuresis was observed in each case as a result of taking thyroid extract; it was most marked and sustained in the case of fracture of the femur, in which the creatinuria was also increased by taking the drug.

### Microbiology and Parasitology

SOME OBSERVATIONS ON THE DEVELOPMENT OF PULMONARY TUBERCULOSIS IN LOWER ANIMALS AS COMPARED AND CONTRASTED WITH SIMILAR LESIONS IN MAN. HERBERT FOX, *Am. Rev. Tuberc.* **17**:435, 1928.

The exact homolog of the history and anatomic development of tuberculosis in man is not found among the lower animals, so that great caution must be used in deducing from animal experimentation how the human disease arises. On the other hand, there is a strong similarity between tuberculosis in wild and in domestic *Ungulata*. On the whole, it seems best to consider that each order of animal exhibits a receptivity as a peculiarity. Ordinate receptivity or susceptibility is a distinct feature of the disease tuberculosis. Zoological family receptivity is likewise important, perhaps more so than is ordinate. Some families of primates are more susceptible than others, and this is also true in the families of the orders *Carnivora* and *Rodentia*. *Ungulata*, to which the domestic cow belongs, show the same type of morbid lesions in all the families, and it is believed that all families are about equally susceptible, even though some, *Tapiridae*, have not been seen with the disease by the author. Lower animals behave in a definite manner when they meet the tubercle bacillus for the first time. There is no true healing, as occurs in man. Certain varieties of animals, the kangaroos, for example, do not seem to have receptivity for the bacillus. In the face of the facts learned from animals, the thought that the human being reacts in a peculiar characteristic manner because he has a definite type of reactivity cannot be dismissed until the identical reaction of the domestic and wild bovine is explained. *Carnivora* react like human beings; certain primates react like youthful human beings and other primates do not react at all. It seems, therefore, that the individual peculiarity of an order, family or genus must play a large rôle in the inception, development and result of tuberculous infection. Infection early in life and recovery therefrom will not explain chronic ulcerative tuberculosis in carnivores or chronic calcareo-caseous lesions in bovine, nor will it satisfactorily settle variations in dispositions in families of the same order. It seems, therefore, that human phthisis is a specific type of receptivity for the bacillus and not the result of acquired immunity, and the calcareo-caseous morbid anatomy of bovine is peculiar to them, and so on through the groups. These data also strongly support the thought that infection may occur at any age and that the hygiene of animals must guard adults as well as young.

H. J. CORPER.

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT ON INOCULATION WITH LEPROSY BACILLI. EDGAR JONES and W. O. TIRRILL, JR., *Am. Rev. Tuberc.* **17:522**, 1928.

Leprosy bacilli, when given in large amounts, stimulate the hematopoietic tissues of the rabbit to a temporarily increased production of both lymphocytes and monocytes. The stimulation occurs in spite of the fact that a definite infection of the animals did not occur.

H. J. CORPER.

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT FOLLOWING INOCULATION WITH SMEGMA BACILLI. LEO SCHWARTZ, JR., and R. S. CUNNINGHAM, *Am. Rev. Tuberc.* **17:537**, 1928.

The object of the experiments was to determine whether the reaction of the rabbit to smegma bacilli had any common factors with those seen after inoculation with virulent tubercle bacilli. The results are categorically definite in showing that there is at least one clearcut similarity in the two types of infection, that is, the increase in the number of the monocytes of the circulating blood and tissues, and the modification of these in the direction of the so-called epithelioid cells. That the smegma bacillus is not especially toxic is amply indicated by the long course pursued by some of these animals without any change in the blood counts; however, when sufficiently large numbers of micro-organisms were injected the animals developed massive lesions of the lungs and other tissues and finally died from the effects of the lesion. In studying the epithelioid cells it was noted that while the bacilli had been phagocytosed in large numbers, most of them were surrounded by neutral red vacuoles, a possible beginning degeneration of bacilli.

H. J. CORPER.

TUBERCULOUS INFECTION OF THE LUNG IN EARLY INFANCY. JEROME L. KOHN, *Am. Rev. Tuberc.* **17:565**, 1928.

A case is presented of tuberculosis in an infant, aged 12 weeks, who was probably infected six weeks before the onset. The Pirquet reaction was positive at 12 weeks, and the first symptoms appeared at 9 weeks of age. The clinical picture simulated that of obstruction by a foreign body or thymic compression. The development and recession of the disease was noted by means of serial roentgenograms. The primary focus (Ghon) was first observed when the child was 3 years and 2 months old. The source of infection was never definitely ascertained. The prognosis of tuberculosis even in early infancy is not necessarily fatal. This child developed normally and was in excellent health more than five years after it first came under observation.

H. J. CORPER.

TUBERCULOSIS OF THE ANTERIOR MEDIASTINAL LYMPH NODES. RICHARD C. BUCKLEY, *Am. Rev. Tuberc.* **17:583**, 1928.

Tuberculosis involving the anterior mediastinal lymph nodes is uncommon. Among 115 cases of pulmonary tuberculosis the author observed the condition in 2 cases, both of which were unusual. In the first case one of the lymph nodes was attached to the parietal pericardium and had ruptured into the pericardial sac, and a tuberculous pericarditis resulted. In the second case, which is reported, the condition simulated an aneurysm of the aorta or a mediastinal tumor.

H. J. CORPER.

MODERN CONCEPTS IN THE PATHOLOGY OF TUBERCULOSIS. MAX PINNER, *Am. Rev. Tuberc.* **17:601**, 1928.

The author points out that it is not in the nature of this analysis to arrive at conclusions but notes that a few points, however, are clearly brought out: 1. The necessity of a terminologic understanding is paramount. 2. In human

pathologic changes, at least, the relation of allergy to immunity is obscure. 3. The allergic condition of the host cannot satisfactorily explain the occurrence of productive and of exudative lesions at the site of reinfection or metastasis. 4. Productive and exudative lesions, immunologically speaking, are not necessarily antagonistic: either may heal, and either may progress. 5. The immunologic conditions under which healing or progression occurs are not well understood. 6. Important, though not exclusive, factors which determine the productive or exudative development of a lesion are hypersensitiveness and resistance to bacilli and localization and dosage of bacilli; a number of secondary factors must be considered.

H. J. CORPER.

THREE CASES OF STREPTOCOCCIC PUERPERAL INFECTION WITH UNUSUAL LESIONS. JOHN W. HARRIS and J. HOWARD BROWN, Bull. Johns Hopkins Hosp. 43:26, 1928.

Three unusual cases of streptococcic puerperal infection are reported: 1. A case of miliary abscesses of the uterine wall in which hysterectomy was performed and in which the streptococcus was recovered from the uterine cavity. 2. A case of postabortal, bilateral thrombophlebitis in which the affected veins were ligated and in which identical streptococci were recovered from the uterine cavity and blood stream. 3. A case of puerperal endometritis, extensive encapsulated peritonitis and embolic pneumonia in which the same streptococcus was recovered from the uterus and from the peritoneal and pulmonary exudates. The streptococci found in these three patients were of three different strains, as shown by the differences in fermentation reactions. According to Holman's classification, the organism from the first case was *Streptococcus infrequens*, and those from the last two cases were *Streptococcus pyogenes*. Further differentiated by Brown's classification, the first two streptococci were atypical members of the infrequens and pyogenes groups, while the last was a typical *Streptococcus pyogenes*.

AUTHORS' SUMMARY.

THE BACTERIAL CONTENT OF THE VAGINA AND UTERUS ON THE FIFTH DAY OF THE NORMAL PUERPERIUM. JOHN W. HARRIS and J. HOWARD BROWN, Bull. Johns Hopkins Hosp. 43:190, 1928.

In thirty uteruses cultured on the fifth day of the normal afebrile puerperium, only ten were found sterile, but none contained streptococci. Vaginal cultures taken at the same time showed the presence of aerobic and anaerobic alpha and gamma streptococci in twenty-four of the thirty patients, but the aerobic, beta-hemolytic streptococcus, which is the etiologic factor in the majority of fatal cases of puerperal infection, was not present in any of the patients studied.

AUTHORS' SUMMARY.

EXPERIMENTAL STREPTOCOCCUS NECROSIS OF THE LIVER. R. N. NYE, J. Clin. Investigation 6:27, 1928.

Intravenous injection into rabbits of bacteria-free filtrates of a certain strain of *Streptococcus scarlatinae* resulted in death. The toxin was relatively thermostable and could be neutralized by scarlet fever antitoxin. It was found in only one of five strains of *S. scarlatinae*. The most marked pathologic change in the killed rabbits consisted of areas of necrosis of the liver, similar to toxic necrosis of the liver seen in human cases. Frequent mitoses in the suprarenals and kidneys suggested damage to those organs.

AUTHOR'S SUMMARY.

HYDROLYSIS OF BACTERIAL PROTEIN DURING LYSIS BY BACTERIOPHAGE. D. M. HETLER and J. BRONFENBRENNER, J. Exper. Med. 48:269, 1928.

During the process of lysis by bacteriophage, there is an appreciable increase in the amount of free amino-acid present in the culture. The increase of free amino-acid is due to hydrolysis of bacterial protein.

AUTHORS' SUMMARY.

TOXIN PRODUCTION BY NORMAL AND BY PHAGE-RESISTANT SHIGA DYSENTERY BACILLI. RALPH S. MUCKENFUSS and CHARLES KORB, J. Exper. Med. **48**:277, 1928.

The production of exotoxin and of endotoxin by normal Shiga dysentery bacilli and by strains resistant to Laudman phage was found to be the same. The presence of phage did not alter toxin production by the resistant organism.

AUTHORS' SUMMARY.

THE INFLUENCE OF CHOLESTEROL ON EXPERIMENTAL TUBERCULOSIS. RICHARD E. SHOPE, J. Exper. Med. **48**:321, 1928.

Cholesterol, administered intraperitoneally in these experiments, definitely prolonged the lives of tuberculous guinea-pigs when the infection was of an acute type produced by inoculation with a small dose of virulent human type organisms. Intraperitoneally administered cholesterol did not definitely prolong the lives of tuberculous guinea-pigs when the infection was of the chronic type produced by the injection of a small dose of human type tubercle bacilli of relatively low virulence, or when the infection was more acute owing to the injection of a large dose of organisms of low virulence. It had no beneficial effect on an acute type of infection produced by the bovine type organism. Cholesteryl chloride, cholesteryl toluide, cholesteryl anilide, sodium cholesterol sulphate and quinine cholesterylolate did not significantly prolong the lives of tuberculous guinea-pigs. Sodium cholesterylolate, in optimal dosage, definitely prolonged the lives of tuberculous guinea-pigs. There was a significant shortening in the duration of life of tuberculous guinea-pigs subjected to the trauma of intraperitoneal injection and repeated handling as compared with tuberculous guinea-pigs that were not handled or traumatized by intraperitoneal injections.

AUTHOR'S SUMMARY.

RECIPROCAL EFFECTS OF CONCOMITANT INFECTIONS. LOUISE PEARCE, J. Exper. Med. **48**:363, 1928.

An experiment is reported in which was studied the effects of a concomitant vaccinal infection and of vaccinal immunity on the reaction to syphilis in rabbits induced by intracutaneous inoculation. The results obtained showed that the reaction was modified by both conditions. A vaccinal infection initiated at the time of syphilitic inoculation was associated with a defensive reaction of lessened efficiency, the ensuing syphilis being more severe than in control animals. A state of vaccinal immunity present at the time of syphilitic inoculation was associated with a reaction of heightened efficiency, the ensuing syphilis being mild. These results are in harmony with those obtained in other experiments in which the intratesticular route of syphilitic inoculation was employed.

AUTHOR'S SUMMARY.

THE ACTION OF THE LEVADITI STRAIN OF HERPES VIRUS AND OF VACCINE VIRUS IN THE GUINEA-PIG. PETER K. OLITSKY and PERRIN H. LONG, J. Exper. Med. **48**:379, 1928.

Repeated intraperitoneal injections in guinea-pigs of the Levaditi strain of herpes virus do not cause any evidences of infection, yet induce immunity to strong strains of herpes virus.

AUTHORS' SUMMARY.

STUDIES ON INDIFFERENT STREPTOCOCCI. C. H. HITCHCOCK, J. Exper. Med. **48**:393 and 403, 1928.

Serologic study of a large number of strains of indifferent streptococci has revealed the existence of a large homogeneous group to which the designation type 1 has been applied. It is recognized that members of type 1 are not necessarily identical, and that further division into subtypes may be feasible. All strains of



type 1 ferment inulin and salicin. The remaining strains are referred to as belonging to group X. They are distinguished only by their failure to react strongly with type 1 serum. While at present this group must be regarded as quite heterogeneous, further work may reveal the presence of other as yet undefined types now included within its limits. The organisms of this group vary in their fermentative reactions with both inulin and salicin. Indifferent streptococci occur in comparatively the same abundance in the throats of patients suffering from rheumatic fever or early in convalescence from the disease as they do in those who have recovered from the disease, or in those of patients suffering from other diseases. There is a slightly increased incidence of these micro-organisms in the throats of hospital patients as compared with those of normal persons. Type 1 occurs with comparatively equal frequency and abundance in the throats of all four classes of patients studied.

AUTHOR'S SUMMARY.

FURTHER EXPERIMENTS WITH THE INTRADERMAL PNEUMOCOCCUS INFECTION IN RABBITS. KENNETH GOODNER, J. Exper. Med. 48:413, 1928.

The analogy between intradermal infection in rabbits with pneumococcus type 1 and human lobar pneumonia is emphasized. As this disease progresses, the amount of antiserum necessary for cure progresses definitely as if there occurred a progressive accumulation of some toxic or antagonistic substance. The effect of antipneumococcus serum in intradermal pneumococcus infection in rabbits may prove to be of value in standardizing antipneumococcus serum. Rabbits that recover from the normal course of intradermal disease have a pronounced but not permanent immunity. Immunity may also be conferred by single and multiple vaccination.

AUTHOR'S SUMMARY.

THE RÔLE OF STREPTOCOCCI IN EXPERIMENTAL POLIOMYELITIS OF THE MONKEY. PERRIN H. LONG, PETER K. OLITSKY and FRED W. STEWART, J. Exper. Med. 48:431, 1928.

The results of the experiments point to the introduction of streptococci as contaminants into cultures during the grinding of tissues. It was found that while streptococci in some cultures occurred in pure growth in others they were mixed with other ordinary bacterial forms which also often were found in pure culture. Any etiologic relation of the streptococci to poliomyelitis could not be determined.

AUTHORS' SUMMARY.

STUDIES OF ACUTE RESPIRATORY INFECTIONS. W. C. NOBLE, JR., and D. H. BRAINARD, J. Prev. Med. 2:313, 1928.

In healthy persons, an anaerobic gram-negative coccus identical with or similar to *M. gazogenes* occurred so frequently as to constitute part of the normal flora of the nasopharynx; it was often found in large numbers and was twice the predominating species. A gram-negative bacillus was encountered in one healthy subject, but only in small numbers. In colds the gram-negative coccus occurred with little change in frequency, but with an average percentage incidence slightly above that observed in healthy persons. Four gram-positive cocci were isolated from three subjects and two gram-positive bacilli from one. Three other species of gram-negative bacilli were found, all differing from the organism encountered in the normal subject. The gram-positive cocci and the gram-positive and gram-negative bacilli occurred infrequently and in small numbers.

AUTHORS' SUMMARY.

EMPHYSEMA IN A CHILD THREE DAYS OLD. GLADYS H. DODDS, J. Obst. & Gynec. Brit. Emp. 35:131, 1928.

A primipara having a moderately prolonged labor and membranes ruptured six hours prior to delivery gave birth to a 8½ months, poorly developed child,

weighing 2,600 Gm. The child became progressively worse and died after eighty-seven hours. Free pus was found in both pleural cavities, and the culture showed a mixed growth of pneumococcus and staphylococcus. The lung showed extensive pneumonia. Among other factors, the prolonged period of ruptured membranes is considered as a source whereby the organisms in the vaginal tube are allowed free access to the fetus, thus permitting aspiration by the fetus.

A. J. KOBAK.

PULMONARY AND BRONCHIAL GLAND TUBERCULOSIS IN INFANCY AND CHILDHOOD. P. F. ARMAND-DELILLE and C. LESTOCQUOY, *Tubercle* 9:359, 1928.

Tuberculous bronchial glands are always enlarged. These enlargements frequently occur in the middle of the mediastinum. Their shadows can rarely be observed in the x-ray plate because they are usually masked by the shadows of the heart, aorta and the superior vena cava. The so-called perihilar shadows are not produced by the glands, for these can give rise only to juxtatracheal shadows. The primary inoculation (chancre d'inoculation) demonstrable in nearly every case after patient search of postmortem sections is only exceptionally detectable in the x-ray picture. A good x-ray plate (a fluoroscope is insufficient) may reveal the presence of miliary tuberculosis early in the course of the disease, often before any other characteristic signs or symptoms have appeared. Pictures taken during the early stages of the disease may show localized lobar shadows persisting for months. An almost identical shadow can be given by primary hepatization, secondary hepatization, caseation and even by splenopneumonia, while sections show that what may have been considered a perihilar condensation in reality corresponds to the first stages of a lobar bronchopneumonic invasion. Roentgenography, in series, shows that in some cases the shadows can progressively disappear, even though it has been possible to demonstrate tubercle bacilli in the sputum. The cases in which healing occurs are rare, and progression is common.

H. J. CORPER.

INTESTINAL TUBERCULOSIS. M. J. STEWART, *Tubercle* 9:409, 1928.

There are only two important varieties of intestinal tuberculosis: one secondary and usually a complication of pulmonary phthisis; the other, hyperplastic tuberculosis, apparently in most cases a primary infection. In typical examples, the pathologic process in these two lesions varies enormously. Secondary tuberculosis is usually frankly ulcerative and shows at the advancing margin the characteristic histology of the tubercle follicle with abundant giant cell systems and caseation. There is little reactive fibrosis, and the muscular coat is rarely penetrated completely. As a rule the ulceration is widespread, extending upward and downward from the seat of election, the ileocecum. In contradistinction to the hyperplastic type, secondary intestinal tuberculosis rarely gives rise to serious obstruction. Strictures, when they occur, are often multiple, and are usually situated in the small intestine. Primary hyperplastic tuberculosis of the intestine is rare in America and more prevalent in European countries. The author reports twenty-one cases of his own in which the treatment was surgical. The lesion is essentially proliferative, and ulceration, while often or even usually present, is not as a rule the conspicuous feature which it is in the secondary type. The walls of the affected portion of the intestine become greatly thickened and hardened, all coats being involved. Of the twenty-one cases, eighteen were histologically tuberculous, two showed tubercle follicles only in the associated lymph glands, while in one tuberculosis was entirely absent. Hyperplastic tuberculosis is a disease of the ileocecal region; it is usually confined to the last foot of the ileum, the ileocecal valve, the cecum or the ascending colon, any or all of which may be involved. Stenosis is most frequent at the lower end of the ileum but occurs in the ascending colon. Occasionally there is much epithelial proliferation, with the formation of true adenomatous polypi. Occasionally, the appendix is involved. Three factors are suggested in explanation of the peculiar tuberculous lesion in primary hyper-

plastic tuberculosis: (1) a fairly high grade of immunity; (2) infection by small numbers of bacteria, and (3) infection by bacteria of low virulence, in many cases bovine.

H. J. CORPER.

FUSOSPIROCHETAL DISEASES OF THE LUNGS. DAVID T. SMITH, *Tubercle* 9:420, 1928.

Various studies indicate that pulmonary gangrene, most cases of pulmonary abscess, certain types of unresolved pneumonia, and bloody bronchitis, putrid bronchitis and chronic bronchiectases are not separate disease entities but different manifestations of infection with an anaerobic group of organisms acting in symbiosis. This group of organisms include: (1) spirochetes (*Treponema microdentium*, *Treponema macrodentium*, *Spirochaeta vincenti* and *Spirochaeta bronchialis*); (2) fusiform bacilli; (3) vibrios, and (4) cocci. These forms are constantly present (1) in the washed pulmonary sputum and (2) in the pulmonary tissue at necropsy, and have been found (3) in the pulmonary tissues of animals dying of the disease transmitted to them by injection of the sputum from patients with abscess and bronchiectasis. Similar organisms are normally present in the gums of patients with pyorrhea, and these pyorrhea organisms will produce typical pulmonary abscesses when introduced into the trachea of mice, guinea-pigs, rabbits or dogs. The patients' own gums are probably the most common source of infection, although infection of the pharynx with Vincent's angina may be a source of danger to others as well as to the patient. Rest in bed, postural drainage and arsenical therapy in the early stages, and skilful surgical intervention in the resistant cases will produce a fairly good percentage of cures. Proper oral hygiene is the most important preventive factor.

H. J. CORPER.

YEASTS AND SPRUE. F. P. MACKIE and G. D. CHITRE, *Indian Medical Research Memoir* 11, Supplement to *Indian J. M. Research*, 1928.

In Bombay, *M. psilosis* (Ashfordi) has been found present in 40 per cent of cases of sprue; it has been found in similar frequency in intestinal diseases (not sprue) in other miscellaneous diseases, and in healthy men and animals; there is no evidence to show that it, or any other of the yeasts studied, has any causative relation to sprue.

AUTHORS' SUMMARY.

EXPERIMENTAL NOCARDIASIS. PIERO REDAELLI, *Bol. dell' Istituto Sieroterapico Milanese* 7:121, 1928.

The author, making use of *Nocardia sanfelicei* N. Sp., studied the primary infection and the cellular factor of natural immunity in receptive animals (guinea-pigs, rabbits), in less receptive animals (dogs) and in refractory animals (fowls).

In receptive, less receptive and refractory animals, the method of the development of the inflammatory process is the same. It is possible to distinguish clearly the diverse moments of the process of reaction, at first of an exudative character and which culminates in the formation of the characteristic and typical nocardiac granule. The stages through which the parasite passes are different just as the moments of the inflammatory reaction of the organism are different. The inflammatory productive phenomena are accompanied by degenerative processes.

The fundamental difference between cellular defense in receptive, less receptive and refractory animals lies in a more ready reaction on the part of the less receptive and refractory organisms, in the acceleration of the rhythm during development of the different periods of the inflammatory process, in a more rapid attainment to that stage in which the specific systems of defense are developed and, therefore, in a more rapid exhaustion of the disease in refractory animals and in the passage of the disease to the chronic state in animals which are less receptive.

A. J. SALLE.

THE CHANGES OF NEUTROPHILE GRANULES IN INFECTIOUS DISEASES. ANTOINE SANDELS, *Jahrb. f. Kinderh.* **120**:196, 1928.

On the basis of the demonstrations of Mommer that normal neutrophilic leukocyte granules disappear at a  $p_H$  of 5.35 while those which are formed by the influence of the toxins of certain infectious diseases (scarlet fever, croupous pneumonia) do not, Sandels studied the character of the occurrence of such pathologic granules in instances of diphtheria, measles, grip, angina follicularis, typhus abdominalis, dysentery, tuberculous meningitis and influenzal meningitis. In all of the acute infectious diseases, the "toxic" granules made their appearance some time after the onset of the disease, reaching a maximum in from five to nine days. In some instances as much as 80 per cent of the leukocytes contained these pathologic granules. Sandels pointed out that a fall in the absolute count of the leukocytes goes hand in hand with an increase in the "pathologic granules." He also observed that there was a decrease in number accompanying an increase in the severity of the disease and before death. He regards them as the result of a physico-chemical process, a probable coagulation or precipitation of the neutrophilic protoplasm in the circulating blood.

FRANK R. MENNE.

METAL SALT THERAPY AND PROPHYLAXIS IN TUBERCULOSIS. L. E. WALBUM, *Ztschr. f. Tuberk.* **51**:209, 1928.

Rabbits were infected intravenously with 0.0001 mg. of moist bovine bacilli of high virulence. The metal salt therapy was started thirty-three days following the infection. The following metals and salts were tested: Cadmium, manganese, "cadmium-complex," cerium, barium, aluminum, lanthanum, molybdenum, platinum, beryllium, zinc, indium, silver, mercury, arsenic, erbium, tungsten, ruthenium, selenium, gold chloride, sodium aurothiosulphate in large and small dosage, 4 amino-2 auro-thiophenol carbonic acid and sodium fluorid. The best therapeutic action was found in cadmium and manganese. Definite but less effective action was found in cerium, barium, aluminum, lanthanum, molybdenum and platinum. All the other materials were not therapeutically active. Similar experiments were performed on tuberculous guinea-pigs. All animals, with the exception of one, died of tuberculosis. Normal rabbits and goats were treated with cadmium and infected later. They all developed tuberculosis, but this was of a benign type and healed finally. Guinea-pigs could not be protected against a later infection, but their natural resistance toward tuberculosis was definitely increased.

MAX PINNER.

DISINFECTION WITH FORMALDEHYDE IN AQUEOUS SOLUTION AND IN GASEOUS FORM IN TUBERCULOSIS. E. BERGIN, *Ztschr. f. Tuberk.* **51**:306, 1928.

Tubercle bacilli were killed in sputum exposed to a highly concentrated formaldehyde water vapor at a temperature of from 62 to 63 degrees for two hours.

MAX PINNER.

THE NUMBER OF BACILLI IN CULTURES OF TUBERCLE BACILLI. W. BLUMENBERG and H. WIENING, *Ztschr. f. Tuberk.* **51**:417, 1928.

Even suspensions of tubercle bacilli, which are free of clumps, can be obtained by using a 15 molar solution of sodium oxalate to which a sufficient amount of sodium carbonate is added to obtain a  $p_H$  of from 8.5 to 8.7. The action of the sodium oxalate is due to two factors, namely, the decrease of surface tension and the precipitation of calcium compounds. Suspensions prepared by this diluent were counted in Bürker's counting chamber. The counting was done in the dark field. The entire apparatus and the solutions must be specially prepared so as to be completely free of formed elements with the exception of the bacilli. Numerous counts indicate that the number of bacilli contained in 1 mg. of moist bacillary mass



is always above one billion and may be as high as four billions. The number of individual cells depends on the nature of the strain, on the medium on which it is grown and on the age of the colony.

MAX PINNER.

INVESTIGATION OF FORMS OF *B. COLI* OCCURRING IN MAN. OTTO MIKKELSEN, Copenhagen, Kandrup & Wunsch, Printers, 1927, Pp. 150. In Danish.

The author studied 185 strains from the urinary tract of 180 patients as well as strains from normal feces. No fixed relation was found between urinary infections and fermentative or serologic types of *B. coli*. It appears that certain definite fecal strains under suitable conditions may cause urinary infections.

### Immunology

RESPIRATORY IMMUNITY IN RABBITS. CARROLL G. BULL and C. M. MCKEE, Am. J. Hyg. 8:477, 1928.

Observations are given which emphasize the fact that bacteria and their specific products readily pass through the mucous membrane of the upper air passages. Systemic effects always were found to follow the presence of bacteria on the mucous membrane of the upper air passages in rabbits, although local effects were not always demonstrable.

PEARL ZEEK.

RESPIRATORY IMMUNITY IN RABBITS. G. HOWARD BAILEY and S. C. CHENG, Am. J. Hyg. 8:485, 1928.

Injection into rabbits of heat-killed cultures of *Bacterium lepi-septicum* exerted a marked protective influence against that organism. Rabbits with subcutaneous or joint abscesses appeared to be immune to intranasal or pulmonary infection with that organism. Previous carriers were more resistant to subsequent inoculation of the organism. The results of the experiments varied in some instances as the ordinary mucoid strain of *Bacterium lepi-septicum* or the virulent D type of that organism was used.

PEARL ZEEK.

RESPIRATORY IMMUNITY IN RABBITS. C. G. BULL and C. M. MCKEE, Am. J. Hyg. 8:723, 1928.

Pneumococci are able to "settle," live and multiply on the nasal mucosa of normal nonimmunized rabbits for only a limited time. Immunized rabbits do not become carriers. The carrier state ends with the appearance of antibodies in the body fluids.

*Bacillus bronchisepticus* may be carried for a long time, although the carrier state stimulates the production of antibodies within a few days. Immunized rabbits may readily become carriers.

The difference in the effect of immunity on the carrier state in the case of these two organisms is thought possibly to be caused by a difference in the nature of the antibodies stimulated by them.

PEARL ZEEK.

PATHOGENESIS AND RECOVERY IN ERYSIPELAS. T. FRANCIS, JR., J. Clin. Investigation 6:221, 1928.

Skin reactions were studied in patients at intervals, and the blood in different stages of the disease was tested for toxin by injecting serum into the skin of susceptible and resistant persons. Neutralization tests were made with the serum of patients and the specific toxin. The results are regarded as indicating a tendency toward increasing reactivity of the skin during convalescence, the absence of a demonstrable toxin in the blood of patients in the acute stage of the disease, and the neutralization of erysipelas toxin by the serum of most patients in the acute stage of the disease with the loss of this power during convalescence.

H. R. FISHBACK.

SEROLOGIC TYPES OF CLOSTRIDIUM TETANI. GEORGE E. COLEMAN and JANET B. GUNNISON, J. Infect. Dis. **43**:184, 1928.

The results of agglutination and absorption tests indicate that there are at least nine distinct serologic types of *Clostridium tetani*.

AUTHORS' SUMMARY.

RHEUMATIC FEVER. 2. ALLERGIC REACTIONS WITH A TOXIN-PRODUCING STRAIN OF THE NONMETHEMOGLOBINFORMING STREPTOCOCCUS ISOLATED FROM RHEUMATIC FEVER. KONRAD E. BIRKHAUG, J. Infect. Dis. **43**:280, 1928.

Guinea-pigs and rabbits sensitized to the nonmethemoglobin-forming streptococcus isolated from patients with rheumatic fever may be rendered cutaneously hypersensitive to filtrates of cultures of this organism. A brief period of specificity in the sensitive state is recorded. This period is shortly followed by a sensitive state that is nonspecific. During this phase of the cutaneous reactions, the allergenic property of the filtrate can be nullified completely with specific antisera. After the end of the cutaneous allergy of this first phase, continued sensitization of the animals with living nonmethemoglobin-forming streptococci produces the reappearance of cutaneous allergy. During the second phase, the reactions of allergy are nonspecific and the allergic principle of the filtrate is nonneutralizable with specific antisera. For this phase, filtrates heated at 98 C. for four hours are not inactivated as allergic substances. Heterogeneity in the cutaneous responses of patients with rheumatic fever to filtrates of the nonmethemoglobin-forming streptococcus and to certain strains of *Streptococcus viridans* might be explained on the basis of prolonged sensitization to any one dominant strain of the non-hemolytic streptococci. Desensitization of bacterially hyperallergic guinea-pigs and rabbits was accomplished during the second phase of cutaneous allergy by intracardial or intravenous injections of bacterial filtrates.

AUTHOR'S SUMMARY.

ANTIGENIC ANALYSIS OF STRAINS OF BACILLUS TYPHOSUS. LEON C. HAVENS, J. Infect. Dis. **43**:335, 1928.

The antigenic identity of strains of *B. typhosus* has been studied by agglutinin absorption, complement fixation and bactericidal activity. The greatest differences between strains were obtained by agglutinin absorption with fractional doses. Complement-fixation and bactericidal tests indicated only minor differences between the strains tested.

Agglutinin absorption is probably the most sensitive method of bringing out differences in antigenic composition. The results indicate that the method is more delicate than practical uses demand. The suitability of a particular culture for the Widal test or for vaccine cannot be definitely determined by means of these experiments, but they indicate that complement fixation and bactericidal tests conform most closely to the empirical evidence gained from practical application in the field.

AUTHOR'S SUMMARY.

BIOLOGIC AND SEROLOGIC STUDIES OF STREPTOCOCCUS CARDIOARTHRITIS. WILLIAM A. KREIDLER, J. Infect. Dis. **43**:415, 1928.

The 107 strains of *Streptococcus cardio-arthritis* studied, exhibited a marked uniformity in their biologic reactions. All fermented dextrose sucrose, inulin, salicin and raffinose; none fermented mannitol. Twenty-one strains (19.6 per cent) failed to ferment lactose and failed to produce acid in milk. None liquefied gelatin or produced indol.

Antigens prepared from each of the strains were agglutinated by a monovalent antiserum of *S. cardio-arthritis* in dilutions high enough to indicate that these strains fall into a definite serologic group and that group agglutinins play but a small part in the results obtained. When the foregoing facts are considered,

there seems to be reason for the belief that these micro-organisms biologically and serologically form a compact species of streptococci. The failure of some of the strains to ferment lactose and the difference in the agglutinability of the strains, suggest that there may exist, within the species, immunologic subtypes of *Streptococcus cardio-arthritis*.

## AUTHOR'S SUMMARY.

THE APPROXIMATION OF THE TOXICITY OF DIPHTHERIA TOXIN IN VITRO.  
ARTHUR LOCKE AND E. R. MAIN, J. Infect. Dis. 43:420, 1928.

A simple, practicable method is reported, whereby the  $L_0$  titer of an unmodified diphtheria toxin may be predicted, in vitro, with an accuracy of from 85 to 95 per cent. The method is based on the use of a formula correlating the properties of toxicity and antitoxin-binding avidity. It consists of a modified flocculation titration, wherein the latter property is evaluated in terms of  $L_1$  titer and "unit flocculation time;" the results being converted into toxicity units by reference to the basic formula.

## AUTHORS' SUMMARY.

SENSITIZATION AND IMMUNIZATION WITH BACTERIOPHAGE IN EXPERIMENTAL PLAGUE. ARTHUR COMPTON, J. Infect. Dis. 43:448, 1928.

Treatment of experimental plague by subcutaneous injection of a weak phage after infection is without any curative effect. The prophylactic use of such a phage, however, is occasionally attended by a partial protection, sufficient to prolong life but insufficient to save the animal. The partially protected animal does not die of phage-resistant, but of ordinary phage-susceptible, plague bacilli. Better prophylaxis results from two interspaced subcutaneous inoculations of antiplague bacteriophage than from one. Actually, after two inoculations of phage, at six days' interval, 40 per cent of such highly susceptible animals as mice showed absolute immunity. No immunity whatever, but instead increased susceptibility to infection followed the prophylactic use of stock vaccine under similar conditions. Marked hypersensitivity to infection (sensitization) attends a limited proportion of the animals undergoing phage immunization, their early deaths being apparently part of a process the end-result of which is the establishment of absolute immunity among a certain other proportion of the animals.

Weak phage, subcutaneously inoculated, is apparently suppressed by the tissues, in this respect recalling the suppression of a weak herpesencephalitis virus by the brain tissue of the rabbit or guinea-pig. Failure to detect the presence of any active phage in the excreta and blood of animals exhibiting absolute immunity after phage inoculations, leads to the tentative conclusion that the immunity in question is probably fundamentally antibacterial rather than protobiotic in nature.

## AUTHOR'S SUMMARY.

THE OPSONIFICATION TEST FOR THE RAPID IDENTIFICATION OF THE STREPTOCOCCUS OF SCARLET FEVER. KATHARINE M. HOWELL and MARIE WERNER, J. Infect. Dis. 43:525, 1928.

Although the opsonification test for the identification of scarlet fever streptococci is not absolutely specific in our series, it nevertheless offers a rapid, valuable aid in the diagnosis of scarlet fever.

## AUTHORS' SUMMARY.

THE UNITS OF PROTECTIVE ANTIBODY IN ANTIPNEUMOCOCCUS SERUM AND ANTIBODY SOLUTION. LLOYD D. FELTON, J. Infect. Dis. 43:531, 1928.

A method is outlined for the standardization of antipneumococcus serum and pneumococcus antibody concentrate. The unit is that fraction of a cubic centimeter of serum or antibody (or dilution) which will protect against one million fatal doses of an eighteen hour serum broth culture of such virulence that from three to ten organisms injected intraperitoneally into a mouse result in death in from thirty-

six to forty-eight hours. In practice 500,000 fatal doses of organisms—0.5 cc. of 1:200 dilution of an eighteen hour serum broth culture in which from three to ten organisms, as estimated by the plate method, are present in a 1:100,000,000 dilution of culture—are used against dilutions of test serum or antibody in a geometric series. By maintaining these units, the reciprocal of the dilution protecting two of three mice represents the number of units in 1 cc. of serum or antibody.

AUTHOR'S SUMMARY.

CONCENTRATION OF PNEUMOCOCCUS ANTIBODY. LLOYD D. FELTON, J. Infect. Dis. 43:543, 1928.

A method for the concentration of the protective substance in antipneumococcus horse serum has been given. Anhydrous sodium sulphate in 20 per cent concentration is used as precipitating agent. The usual technic for filtering and dialyzing the "cake" is employed. The contents of the sac, euglobulin, pseudoglobulin and protective substance, are adjusted to  $p_H$  4.6 to 4.8, at which point a precipitate is formed containing an inert protein (euglobulin?) along with a quantity of lipoids. This precipitate is removed and the clear supernatant (pseudoglobulin, protective substance, some euglobulin and albumin) is adjusted to  $p_H$  6.8, and diluted 4 or 5-fold with cold distilled water. A white precipitate is thrown down containing practically all the protective substance present in the original serum. This precipitate dissolves readily in sodium chloride, is high in protective power, and for intravenous injection, is practically free from severe chill-producing characteristics.

AUTHOR'S SUMMARY.

IMMUNOLOGICAL INVESTIGATIONS ON TROPICAL SPRUE IN PORTO RICO. CHARLES WEISS and FRANCISCO LANDRÓN, J. Infect. Dis. 43:557, 1928.

The isolation of *Monilia psilosis* from the feces is greatly facilitated by the use of glycerol and bile to inhibit the growth of common fecal bacteria. With this technic the fungus has been obtained from a large percentage of both cases of sprue and control subjects. *M. psilosis* grows in both liquid and solid mediums over a wide  $p_H$  range with an optimum of  $p_H$  7 in infusion broth. In liquid mediums of low  $p_H$ , growth brings a progressive alkalinity approaching  $p_H$  8, the apparent optimum for survival. These observations are not in harmony with the idea that an increased acidity of the intestinal contents favors the establishment of the fungus. Intravenous injection of *M. psilosis* kills rabbits in from a few minutes to forty-eight hours, the time depending on the dose. In the later deaths visceral embolic lesions containing the fungus are found. *M. albicans* and a cryptococcus of blastomycosis act similarly. *M. psilosis* and the two related fungi contain endotoxins, which, however, are not hemolytic and are not specifically antigenic when tested intradermally on immunized rabbits, cases of sprue and human controls. A filtrable nonhemolytic exotoxin can also be demonstrated in each of the three fungi.

These observations do not support the theory that *M. psilosis* is an etiologic factor in tropical sprue.

AUTHORS' SUMMARY.

THE PREPARATION OF ANTIGENIC SPECIFIC SUBSTANCE FROM STAPHYLOCOCCUS PYOGENES AUREUS. H. B. DAY, Brit. J. Exper. Path. 9:198, 1928.

Experiments are described in detail which prove that the specific substance from staphylococci is liberated in an active antigenic state. Complete loss of activity follows unless the free specific antigen is protected from the action of living cocci and their enzymes. This destructive effect is not immediate, so that it is possible to obtain active specific substance, from staphylococci undergoing rapid autolysis, by methods which ensure prompt sterilization and cessation of further enzyme cleavage. The best results are obtained by extracting staphylococci at a temperature which destroys enzymes.

AUTHOR'S SUMMARY.



IMMUNITY AND ALLERGY IN THE PATHOGENESIS OF TUBERCULOSIS. ALLEN K. KRAUSE, *Tubercle* 10:22, 1928.

The author discusses briefly in this article immunity and allergy in tuberculosis, and points out the manner in which allergy creates symptomatology as well as the fact that it leads to immune effects. In every established tuberculous infection we may think of every increase of intrafocal tubercle bacilli, or every conveyance of bacilli beyond their focal bounds as met by allergic reactions. In the vast majority of countless instances the number of bacilli concerned are too small to lead to appreciable or sensible effects. Their fixation, immobilization and perhaps partial or complete destruction are accomplished. This end-result is conceived of as immunity. Large numbers of bacilli originate more severe to florid reactions, when illness, pathogenesis, now features clinically the "effort" to halt the progression of bacilli (infection), that is, to accomplish again what will appear as immunity, if only the patient recovers from the illness. It is further pointed out that fulminating tuberculosis is the expression of intense allerge-immune action, and that immunity and allergy are competent under average conditions.

H. J. CORPER.

RESEARCHES ON THE RESISTANCE OF DIPHTHERIA AND DYSENTERY TOXINS TO DIFFERENT HYDROGEN ION CONCENTRATIONS. C. IONESCO-MIHAIESTI and A. DAMBOVICEANU, *Arch. Roumaines de Path. Exper. et de Microbiol.* 1:115, 1928.

The destruction of these toxins by acid and alkaline solutions was not immediate. Inoculations into guinea-pigs thirty minutes after preparation of the dilutions showed the limits between which diphtheria toxin maintained its activity to be  $p_H$  4.7 to 4.9 and 9.6 to 10.01. After twenty-four hours, the extreme limits of toxicity were 5.7 to 5.9 and 9 to 9.4. With dysentery toxin inoculated into rabbits, thirty minutes after preparation, toxicity was demonstrated between the limits of  $p_H$  2.07 to 2.15 and 11.0. After twenty-four hours, a  $p_H$  of 2.5 to 3 destroyed the toxin completely, while  $p_H$  3 to 3.5 caused attenuation. The limit on the alkaline side could not be determined. It appears that diphtheria toxin is more sensitive to the action of acids and alkalies than is dysentery toxin.

INTERFEROMETRIC AND CHEMICAL DEMONSTRATION OF ABDERHALDEN'S SERUM-FERMENTS. E. KUSTER and K. KOULEN, *Fermentforsch.* 9:265, 1928.

The interferometric method has been suggested for the quantitative determination of Abderhalden's ferments in serum, but the results obtained so far has been irregular. The authors investigated the hypothesis that there are at times ferments in serum which, through decomposition or hydrolytic splitting of added organic substrate, cause an increase in concentration which can be measured with the interferometer.

In sterile serum kept at 37 degrees, an increase in amino-acid nitrogen was demonstrated, but a certain increase in the interferometric value could not be found. The addition of kaolin to the serum did not increase the natural autolysis, even after forty hours incubation. Dialysis of serum against distilled water led to a stronger ninhydrin reaction in the dialysate than dialysis against physiologic solution of sodium chloride, but the increase was no greater than that occurring in serum kept in the incubator for an equal length of time. The autolysis could be attributed either to ferment activity or to a physicochemical process.

Fresh and inactivated serums from pregnant and nonpregnant persons were mixed with placental substance, and the interferometric increase and ninhydrin reactions determined. No constant differences between the serums were found. Since decomposition in active and inactivated serums was frequently the same, the splitting appeared to be to a great extent independent of ferment activity. Further experiments supported the hypothesis of Pregl, that increase in concentration of the mixtures is partly due to swelling of the added organic powder in the serum, with absorption of water. This effect could be avoided by allowing the swelling

to take place previously, according to a method described by Pregl. Even after elimination of this source of error, the action of placental substance on serum revealed a frequent increase in nonprotein nitrogen without relation to changes in the interferometric index. Several serums with marked increase in nitrogen showed but little change in the interferometric value, and vice versa. No constant relationship could be demonstrated between interferometric index and clinical diagnosis, and no clinically significant results were obtained with this method.

The authors found further that organic substrates in alkaline buffer solutions and in serum effect a shift in  $p_H$  toward the acid side. Under these conditions, a part of the substrate went into solution, that is, a purely physical process took place.

B. R. LOVETT.

INHERITANCE OF BLOOD GROUPS. K. H. BAUER, Klin. Wchnschr. 7:1588, 1928.

Bauer presents a theory of blood group inheritance, based on the coupling and the exchange of germinal factors. The term coupling of factors refers to the presence of different factors in the same chromosome. The term exchange of factors refers to the breaking up of this coupling and the separation of factors that have heretofore always been transmitted together. This occurs when there is synapsis of homologous chromosomes, with subsequent separation, in which fragments of one became included in the other. This theory explains the O and AB children of O  $\times$  AB marriages, which Bernstein's theory totally fails to explain, and which Dungern and Hirschfeld's theory would lead one to expect in much greater numbers than they actually appear. In 174 O  $\times$  AB marriages, with 474 children, the latter were found to be distributed among the blood groups as follows: O, 22; A, 216; B, 204; AB, 28.

CHANGES OF THE BLOOD IN SYPHILIS. F. KLOPSTOCK, Klin. Wchnschr. 7:1896, 1928.

The changes of the blood in syphilis are caused by the invasion of the spirochetes. The peculiarity is that a lipoid combination of the spirochete and not a protein substance is the antigen which stimulates immune substances.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF THE BLOOD GROUP AND OF PLASMODIUM SPORULATION ON THE TYPE AND INCUBATION PERIOD OF MALARIA. G. HOPF, München. med. Wchnschr. 75:1755, 1928.

With intravenous transfer of malaria into compatible recipient, there is an incubation period of four days or less. A longer period exists with incompatible bloods. With the transfer of the quotidian type in the last half of the afebrile period, especially three or four hours before the chill, even though the bloods are incompatible there is no delay of the incubation period, but there is a tendency to the tertian type of infection. This is interpreted to mean that the injury caused by the agglutination of the red cells also affects the enclosed plasmodia.

E. F. HIRSCH.

AUTO-ISO-AGGLUTINATION. H. D. E. MILDERS, Nederl. Tijdschr. v. Geneesk. 72:4108, 1928.

In a patient with cirrhosis of the liver a severe internal hemorrhage made blood transfusion necessary. The patient belonged to group O. A donor was found in a brother whose blood group was the same, but when, before operation, the two bloods were brought together, agglutination took place. Furthermore, the patient's serum was found to agglutinate his own blood cells. Pseudo-agglutination was thought of, but ruled out. The patient's serum was then tried out with the blood of other persons belonging to group O. Agglutination took place in every case. The examinations were repeated in a moist chamber at a tempera-

ture of 37 C. Under these conditions the agglutinations no longer took place. The transfusion was carried out and there were no untoward effects. The patient was twice reexamined, two months and five months, respectively, after the transfusion. The phenomenon of auto-agglutination was unchanged. It was found in three other patients with cirrhosis of the liver; in one the blood cells were agglutinated by the ascites fluid as well as by the serum.

### Tumors

INFECTIOUS MYXOMA IN RABBITS. JOSEPH R. HOBBS, *Am. J. Hyg.* **8**:800, 1928.

This condition, which resembles both an infectious process and a tumor growth, is apparently caused by a virus which can be recovered from exudates in the nose, eyes and infected cutaneous tissue. Infection is produced by rubbing the virus material over scarified skin, or by introduction of it into the nasal passages. The virus is filtrable through Berkefeld V filters, but not through Berkefeld N or Chamberland L5 or L7 filters. The virus is present in the blood stream of infected animals. It can be kept infective in pieces of myxomatous tissue in 50 per cent glycerin in the icebox for at least a year. The virus can be destroyed by certain chemicals and by radiation. The response of tissue to infection with it is peculiar to the virus and distinct from the response of tissue of the rabbit to infection with bacteria or protozoa.

PEARL ZECK.

MULE SPINNERS' CANCER. S. A. HENRY, *J. Hyg.* **28**:100, 1928.

The largest number of cases occur after a period of contact of from thirty-five to thirty-nine years (18.6 per cent), though as many as sixty-three years, or possibly more, may sometimes be necessary. It is not essential that the exposure to the carcinogenic agent should be continuous; and the disease may declare itself long after the patient has retired from the industry.

AUTHORS' SUMMARY.

TUMORS OF THE SKIN AND MAMMARY GLAND CAUSED BY PYROGENOUS PRODUCTS OF CHOLESTEROL. E. L. KENNAWAY and BASIL SAMPSON, *J. Path. & Bact.* **31**:609, 1928.

The products obtained by heating cholesterol to about 800 C. caused epithelioma of the skin in mice and a duct papilloma of the mammary gland in a rabbit.

AUTHORS' SUMMARY.

GIANT-CELL TUMORS OF BONE IN A FOWL. S. L. BAKER, *J. Path. & Bact.* **31**:657, 1928.

In this article, the author describes a giant cell tumor at the upper end of the tarsometatarsus of a fowl, which seems to be indistinguishable from the giant cell tumor found in human bones.

THE OXYGEN TENSION NECESSARY FOR THE MITOSIS OF CERTAIN EMBRYONIC AND NEOPLASTIC CELLS. G. PAYLING WRIGHT, *J. Path. & Bact.* **31**:735, 1928.

In tissue cultures, the lowest oxygen tensions at which division of cells takes place are, for myoblasts of chicken heart, about 12 mm. of mercury; for cells of Jensen rat sarcoma, about 6 mm. of mercury, and for cells of mouse carcinoma 2146, about 3 mm. of mercury, corresponding to 1.6, 0.8 and 0.4 per cent of oxygen at atmospheric pressure.

AUTHOR'S SUMMARY.

CHORDOMA OF THE VERTEBRAL COLUMN WITH THREE NEW CASES. D. F. CAPPELL, *J. Path. & Bact.* **31**:797, 1928.

Three cases of chordoma are recorded, in each of which the growth occupied an unusual site in the vertebral column, two occurring in the cervical and one

in the dorsal region. One of these presented interesting histologic features which recapitulate in a striking manner the ontogenetic and phylogenetic evolution of the notochord, a brief outline of which is given. The embryology of the notochord in the human subject has been studied, and certain aberrations of development have been observed which are in agreement with the observations of Peyron and of Linck and Warstadt.

AUTHOR'S SUMMARY.

CHORIO-ANGIOMA. KARL MAYER, Arch. f. Gynäk. 134:482, 1928.

Chorio-angioma, hitherto described under various names, is not an uncommon tumor of the placenta, but nevertheless Mayer believes that a routine study of placentas might uncover more of these tumors. Thus the cause of abortions, prenatal deliveries, polyhydramnios and certain unexplainable neonatal deaths, associated with this tumor, might be cleared up. The growth consists essentially of a blood vessel tumor embedded in a connective tissue matrix. It is easily shelled out. The parenchyma consists of a growth of blood vessel endothelium with typical capillary formations. Mayer gives a detailed description of a case that came under his own observation and reviews the literature.

A. J. KOBAK.

### Medicolegal

SUDDEN DEATH FROM JELLYFISH POISONING IN STATUS LYMPHATICUS. H. W. WADE, Am. J. Trop. Med. 8:233, 1928.

A well developed, healthy young man, with only slight remaining evidences of leprosy, was working waist deep in the water of a mangrove swamp when he called out in distress to fellow workmen nearby that something had bitten him. He quickly collapsed, breathing with difficulty, and died within a very few minutes. Wade could not find any mark suggestive of a snake bite, or any other abnormality except purplish (livid) markings ascribable only to contact with a large, long tentacled jellyfish. The head was livid. The lungs were distended and did not collapse; they contained much frothy serous material that had escaped from the alveolar capillaries. The right side of the heart was full, and the blood was fluid and dark. The viscera were congested, especially the kidneys, which showed parenchymatous injury and albuminous material in the glomerular capsules. The fatal outcome was too sudden to be ascribed to the poisoning alone. Definite evidence of status lymphaticus was found, and it is probably because of the peculiar instability known to exist in this condition that the unquestionably severe shock of the jelly-fish sting induced sudden death.

THE FATE OF MORPHINE INJECTED INTO THE ANIMAL BODY. Y. TERUCHI and S. KAI, J. Pharmacol. & Exper. Therap. 131:177, 1927.

Morphine is not easily destroyed in the animal body. In an examination of the entire body of rabbits into which it was injected from three to sixteen hours before, almost the entire amount was recovered. In suspensions of liver, lungs and kidneys of rabbits outside the body, morphine was not destroyed in four hours at 38 C. Protection against the poison is aided by its storage (about 30 per cent) in muscles and by excretion. Excretion from the blood into the stomach occurs before excretion into the urine, but after some hours they proceed apace. Taken through the liver from the stomach and bowel, the drug may follow the same route again.

In chronic poisoning, the amount stored in muscles is greater, and both excretion and the ability to destroy morphine are augmented. In chronic morphine poisoning, the amount in the blood is larger than in acute poisoning. It is present in plasma and blood cells in equal amounts. In acute poisoning, as much as 90 per cent may be recovered, but in chronic experimental poisoning in rabbits only about one sixth of the amount injected.

E. R. LE COUNT.



OCCUPATIONAL DISORDERS FROM PNEUMATIC TOOLS. E. LONG and F. NAVILLE, *J. de méd. de Lyon* 8:577, 1927.

Observations are reported of the curious symptoms that are produced by the rapid vibrations transmitted to the bodies of laborers from pneumatic tools, and by the constant cold to the hands or other parts exposed to the blast of compressed air. Five cases are described with nothing of moment not covered by a report from the Bureau of Labor at Washington in 1918, based on evidences of this occupational disease in 68 of 100 stonecutters examined. The present report contains an especially interesting discussion of the legal interpretations of what constitutes an accident in different countries, and the need of greater uniformity. One of the five patients was refused award for damages at three separate hearings, notwithstanding the fact that his symptoms persisted for three years after he changed his occupation. Some patients have vasomotor disorders which simulate Raynaud's disease.

E. R. LE COUNT.

UNUSUAL WOUNDS OF THE URINARY BLADDER. HORTOLOMEI, J. *d'urol.* 24:286, 1927.

Abrupt, uncontrollable cessation of urination leading to efforts to urinate from twenty to twenty-five times a day, urination being easier when the patient was sitting or lying down, led to the discovery of an unbruised shrapnel ball free in the bladder and without incrustations. The wound was received six years previously. The symptoms began two years after the injury. In another patient, the wounds of entrance and exit made with a revolver bullet healed without operative intervention. After the acute symptoms had subsided, the wounds were seen cystoscopically.

E. R. LE COUNT.

DISTURBANCES OF LIVER METABOLISM IN CHRONIC ALCOHOLISM. P. BÜCHLER, *Arch. f. Psychiat.* 81:280, 1927.

Many of the minor late effects of the poisonous action of alcoholic beverages are not outspoken disease requiring prompt medical attention. They are vague symptoms, not present all the time, and in the beginning only one or two are evident. They take the form of loss of attention, will power and initiative; inability to concentrate; lowered morale; illusion, and hypnagogic hallucinations. They are commonly referred to under the general designation, chronic alcoholism. A state of prepsychosis or of subdelirium is attained when such symptoms of impaired mentality are numerous and pronounced.

There are two views of the pathogenesis of this chronic alcoholism and of the more clinically definite delirium, psychoses and epilepsy which follow poisoning with alcohol. One explanation is that they are all brought about by action of the alcohol on the liver and hepatotoxins accruing from this action. The other attributes them to generalized disturbance of metabolism and vitiated ferment actions caused by increased oxidation of phosphatides and the resulting ketoacidosis.

Reports of a number of investigations have been made by Büchler. One was a study of the blood in 105 patients, including observations made up to 1925. The results of that examination are included with this report of changes in the blood of forty-five more patients, altogether 150. The evidence of damage, least in persons with the vague symptoms so conveniently disposed of as chronic alcoholism, steadily mounts as disease becomes more clearly evident clinically and is most marked with delirium and severe psychoses.

Fat splitting properties of the blood, said to be due to lipases formed only when the liver is diseased and not inhibited by quinine as are the lipases normally present, were found well developed in persons with the fewest symptoms, 66.7 per cent as compared with the 100 per cent associated with psychoses and delirium. In the poorly defined chronic alcoholism, coagulation of the blood was slower, 20.9 per cent; with psychosis, 31.2 per cent; with delirium, 76.2 per cent.

A third and valuable indication of pathologic disturbances was urobilinogenuria. This condition, reduced to a percentage basis and sought in 140 patients, was 39.3 per cent in simple chronic alcoholism, 48.7 per cent with psychosis and 81.2 per cent when delirium was present.

Other disorders, such as diminished tolerance for galactose, a high serum bilirubin, toxic amines in the blood and hypercholesterinemia, were all more pronounced as the results of alcohol poisoning became more serious. The bilirubin content was only from 1 to 2 mg. per hundred cubic centimeters of blood; Büchler explained this by the lower content of alcohol in the Hungarian wine which was responsible for the conditions he studied. When the beverage was largely brandy, other observers found from 4 to 6 mg. of bilirubin. The indications of grave pathologic metabolism gradually disappear with recovery from delirium, but in the alcoholic psychoses they are more permanent. A congenital abiotrophy of the central nervous system or an abnormal intolerance for alcohol are suggested for the few changes of the blood in 11 per cent of the patients with delirium.

E. R. LE COUNT.

ABORTION WOUNDS. WINTER, *Deutsche med. Wchnschr.* **53**:1931 and 1976, 1927.

This is a long account of how wounds of the uterus are made by physicians, of the more and less dangerous instruments, of how such wounds may be avoided and of safely performed abortions. The article is mainly clinical. But slight reference is made to the injuries inflicted by midwives and worse bunglers, such as are encountered in mediocolegal work. There are interesting references to the literature—to the reports of 357 perforations in the practice of ninety-five physicians of Westphalia and the lower Rhine region, to 2.9 per cent of 443 perforations being made with the finger, to 134 cases during thirteen years—reported by one observer, etc. The small curet is considered the most dangerous tool. Nonpregnant uteri are less often, and those of women many times pregnant most easily, perforated. Winter believes that perforations are made accidentally by physicians more often than in the practice of abortion. Questions of malpractice and of criminal guilt are more common than ever before; likewise, the endeavor to secure monetary indemnification rather than legal punishment.

E. R. LE COUNT.

CHRONIC TRAUMATIC EDEMA. RAESCHKE, *Klin. Wchnschr.* **6**:1763, 1927.

Chronic traumatic edema occurs at all ages, usually involves extremities, may last a few hours or throughout life and has a varying firmness. Lymph accumulates in the tissues, and there may be marked disease of the blood vessels, especially capillaries. In the case reported, the right arm was affected following a crushing injury. At one operation for the edema, the sympathetic nerves were dissected from the brachial artery; at another, all the fascia of the arm and hand down to the finger joints was removed. Finally, the arm was amputated. After this, bad news caused swelling of the stump, but the edema disappeared when the alarm proved groundless. It was then learned that the patient, a man, desired the amputation to obtain indemnification and start a small business.

E. R. LE COUNT.

MYOSITIS OSSIFICANS TRAUMATICA. M. STRAUSS, *Klin. Wchnschr.* **6**:699, 1927.

Four months after the dislocation of one hip, roentgen examination disclosed a mass of spongy bone, extending from the great trochanter of the femur on that side up to the innominate bone. It was in the muscles and unconnected with adjacent bone. A large mass of metaplastic bone caused by trauma, also located about one innominate bone, was described by Eben J. Carey (*Tr. Chicago Path. Soc.* **11**:356, 1923). This case was especially interesting because microscopically a change to sarcoma had occurred in a few places.

E. R. LE COUNT.

POLYNEURITIS FOLLOWING ACUTE THALLIUM POISONING. R. GREVING and O. GAGEL, *Klin. Wchnschr.* **7**:1323, 1928.

A widow, aged 30, attempted to commit suicide by eating, with bread, one-half tube of "Celiopaste," containing a preparation of thallium, used as rat poison. Two days later, she experienced anorexia and cramping sensations in the chest and toes. Ten days later, the left patellar and achilles reflexes were lost, the left ankle and calf were hyperesthetic and the leg, when lifted, felt lifeless. Excruciating pains in the extremities in five attacks lasting from a month to a week were noted during the patient's five months' stay in the hospital. There was a loss of scalp hair on the twelfth day after poisoning and at irregular intervals short attacks of myocarditis. The menses stopped for four months. The noteworthy features of the examinations of the blood were: white cells, 5,500; eosinophils, from 6 to 11 per cent, and lymphocytes, from 28 to 30. Gastric acidity was found to be: free acidity, 6, and total acidity, 15. Experiments on small animals promise a polyneuritis following ingestion of a thallium compound.

GEORGE RUKSTINAT.

THE INCREASING FREQUENCY OF POSTOPERATIVE PULMONARY EMBOLISM. J. OEHLER, *München. med. Wchnschr.* **74**:1662, 1927.

This report was made at a meeting of surgeons of Northwestern Germany in December, 1926. The discussion (*Zentralbl. f. Chir.* **54**:939, 1927) supported Oehler's contention that there has been recently a marked increase in the number of deaths from postoperative pulmonary embolism; Oehler and others believe this increase is due to the administration of various drugs intravenously. Mention is made of calcium chloride urea and of preparations supposed to lessen the likelihood of postoperative pneumonia. Some of these contain calcium and, presumably, promote coagulation of the blood. But the increase in the number of deaths from these causes is not entirely postoperative, for Fahr of Hamburg reported an increase from the intravenous administration of remedies for such nonsurgical conditions as apoplexy and diseases of the heart and blood vessels. During the years 1915 to 1923, Fahr found twenty-four deaths from pulmonary embolism in 1,200 postmortem examinations, with a percentage of from 1 to 4.2 for each year (*Klin. Wchnschr.* **6**:2179, 1927). In the period from 1925 to 1927, however, he encountered 146 in 1,800 postmortem examinations, and of these ninety-five were unconnected with operations. In the discussion of Oehler's paper, statements were made of a falling off in the number of deaths when intravenous medication was discontinued.

E. R. LE COUNT.

DROWNING FROM WATER IN THE EARS. GUTTICH, *München. med. Wchnschr.* **74**:1919, 1927.

Experiments were made with the vestibular caloric reaction in guinea-pigs and in swimmers bathing in an inside pool. With the head out of the water, cold water in one ear causes swimming in a circle, especially when vision is obstructed. With the head under water, a somerset-like tumbling may occur, the head pitching forward. Such reactions may occur with the tympanum intact, but with perforated drum membranes they take place more readily and more promptly. There is little likelihood that the nystagmus will occur while a person is swimming in still water with the head out. The time under water in diving is usually too short for disorientation to become dangerous except when the ear drums are perforated. With animals on land, a corkscrew-like rolling has been produced.

E. R. LE COUNT.

THE MEDICOLEGAL SIGNIFICANCES OF THE CORPUS LUTEUM OF PREGNANCY. H. KATZ, *München. med. Wchnschr.* **75**:1291, 1928.

A divorcee, aged 22, having had illicit relations, noticed that the menstrual period of June was shorter than that of May; the July period was absent.

Because of pain in the lower part of the abdomen, she sought medical attention at a hospital. A cyst of the right ovary was found on examination, and operative removal was advised. The enlargement of the uterus was about that of the second month of pregnancy. The right adnexa, including the ovary with a cyst the size of a pigeon's egg and a well preserved corpus luteum, were removed on July 19. After nine days, the woman left the hospital and for five days thereafter had pain and uterine hemorrhage. Believing herself pregnant and wishing to have an abortion she went to Dr. X, who repeatedly had come to the notice of the authorities because of the suspicion that he had performed abortions. She reported to him that she was pregnant, and he, without further inquiry, made intra-uterine manipulations. When arraigned in court, he excused his uterine intervention on the basis that he believed a hydatid mole was present. This conclusion was reached because he thought the uterus was too small for a nine to ten weeks' pregnancy, as the cervical canal was patent for a little finger; after little dilation, he had inserted, without trouble, a large curet and removed from the cavum only small fragments of brown tissue.

The expert testimony brought out that destruction or removal of the corpus luteum of pregnancy during the early months of pregnancy is likely to result in abortion, and lead to the acceptance of Dr. X's statements and his release by the court.

E. F. HIRSCH.

SYMMETRICAL GANGRENE OF THE FEET FROM PHOSPHORUS POISONING. H. ROSSIER, *Schweiz. med. Wchnschr.* 57:890, 1927.

As a result of melancholy, a young woman took 3.5 Gm. of rat poison; except for a little abdominal distress and vomiting, she was able to perform her work as usual for four days. The abdominal pain then increased, and a small degree of icterus was noticed. On the fifth day, 1 per cent of sugar was found in the urine; that night, pain was noted in the feet which were hot. Pulsation in the arteries of the lower extremities was normal. The next day, the great toes were livid and cold, and gangrene subsequently spread to other toes and the adjacent plantar parts. Death occurred on the tenth day. Phosphorus was not found chemically in material obtained from the body after death. Comment is made on the failure to examine the vomitus and stools before death, and the arteries of the lower extremities at the time of the postmortem examination. There was no hypoglycemia, and the glycosuria followed lowering of the renal threshold for sugar retention. An increased ease of lysis of the patient's red cells in test tubes was also noticed. Icterus became marked; death in coma resulted.

E. R. LE COUNT.

PSYCHIC DISTURBANCES AFTER ATTEMPTED SUICIDAL HANGING. F. SALINGER and H. JACOBSON, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 110:372, 1927.

Different opinions have been advanced regarding the peculiar symptoms which follow strangulation by hanging in persons who have been found in time, cut down and brought back to life. Before consciousness returns, convulsions usually occur, and in many persons these have been followed by a transitory mania. These symptoms have been accepted as results of the cerebral anemia. The controversy has been mainly with the retrograde amnesia, emotional instability and symptoms of psychosis which follow return to consciousness and persist for days. By some, these have been explained as hysteria and as unconnected with changes in the brain due to strangulation. Others have maintained that all the symptoms originate in organic cerebral lesions.

In reporting a case with symptoms lasting three days after the return of consciousness, the authors include an excellent review of the reports of fifteen others, together with the explanations offered. The presentation is conservative, but tends toward explaining everything by organic changes. It seems safe to predict from the outcome of studies made of the brains of persons with similar symptoms from carbon monoxide poisoning, that if the opportunity is presented



to study the brains of persons almost strangled to death, there will be little difficulty in accounting for all the symptoms. Now and then, with carbon monoxide poisoning the approach to death is close and recovery protracted, and a wide range of manifestations of altered mentality and even dementia result. In both conditions, there is deprivation of oxygen and probably poisonous action of substances normally rendered harmless by the usual supply of properly oxygenated blood, or removed by the usual circulation of healthy blood.

E. R. LE COUNT.

PARALYSIS AGITANS AND TRAUMA. E. HENSSGE, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **110**:796, 1927.

Paralysis agitans was first noted three months after a fall in one patient and six months after in a second. One was 42 years old and the other 52, and they were not prematurely senile. The tremors began on the side injured, and accounts of the injuries were thoroughly reliable. Others have commented on the high ratio of trauma with this uncommon disease. The back and forth play of nervous impulses between muscles and the central nervous system, the unusual demands on muscles to maintain equilibrium during falls and minimize injury and the terminal character of the arterioles in basal ganglions and other parts of the brain involved are given as reasons for a causal relationship.

E. R. LE COUNT.

SPONTANEOUS RUPTURE OF THE AORTA DURING LABOR. P. BOHNEN, *Zentralbl. f. Gynäk.* **51**:2398, 1927.

Death in labor, at the ninth month, from a spontaneous transverse rupture of the aorta, 2 cm. distal to the aortic leaflets, is reported. Marked arteriosclerosis and loss of renal parenchyma from chronic disease was noted. According to Bohnen, there are only four similar reports in literature of rupture during labor. According to different authorities, the blood pressure is increased from 60 to 100 mm. of mercury during labor pains.

E. R. LE COUNT.

CORROSION OF THE URINARY BLADDER, DILATED URETERS AND RENAL PELVES FOLLOWING ATTEMPTED ABORTION. R. ANDLER, *Zentralbl. f. Gynäk.* **51**:2921, 1927.

Severe corrosion of the lining of the urinary bladder occasionally results from the injection of solutions through the urethra instead of into the uterus in attempts to produce abortion. Chlorinated lime, soap with pepper and iodine have been used. In Andler's patient, about 20 cc. of a concentrated solution of albumin acetate was tried. The acute symptoms of corrosion lasted many months, and when they improved pain in both kidneys was noted, with tenderness and enlargement of the right kidney. Cystoscopic examination showed that the ureteral mouths were greatly enlarged and funnel-shaped, and roentgen examination after the injection of collargol disclosed marked dilatation of the ureters and renal pelves.

Mention is made of the reports of five other cases of corrosion of the bladder from efforts to cause abortion, with only one abortion actually produced, and of one corrosion as the result of a fear of gonorrhea. With the corrosion of the vesical lining, it is believed that a paralysis of the muscles in the walls of the ureters at their lower ends occurs, and such systolic force as the bladder exerts dilates the ureteral orifices. After this, the dilatation upward of the urinary passages takes place.

E. R. LE COUNT.

## Technical

THE EFFECT OF EXTERNAL TEMPERATURE ON THE SEDIMENTATION RATE OF THE RED BLOOD CORPUSCLES. MURRAY B. GORDAN and DAVID J. COHN, *Am. J. M. Sc.* **176**:211, 1928.

External temperature was found to exert an influence on the sedimentation rate of the red blood cells. Higher temperatures accelerate the rate and lower temperatures diminish it; therefore, the sedimentation test should be performed under controlled temperature conditions.

PEARL ZEEK.

THE PHENOLTETRACHLOROPHTHALEIN TEST OF LIVER FUNCTION IN THE LATER TOXEMIAS OF PREGNANCY. SAUL BERMAN, *Am. J. Obst. & Gynec.* **16**:410, 1928.

Berman concedes that this test has no practical value in late toxemias. One hundred and eighteen cases were investigated. In twenty convulsions occurred and in ten of these cases retention of the dye. Of the six patients who died only three retained any of the dye. Nephritic and pre-eclamptic toxemias could not be differentiated by this test of dye retention. The majority of patients with chronic nephritis did not show retention.

A. J. KOBAC.

THE VALUE OF THE DIAZO TEST OF BLOOD. S. M. RABSON and L. JACOBS, *Arch. Int. Med.* **42**:386, 1928.

The diazo test was positive in 7 of 415 consecutive specimens of blood from a hospital ward, and in 40 specimens from patients with severe cases of nephritis. The test was positive in blood with a low creatinine content and negative with creatinine values of 3 mg. per hundred cubic centimeters of blood or more. Uremia did not always give a positive test, even in the presence of coma. In one case in which there was obstruction of the kidney, the positive reaction became negative on relief from the obstruction.

HAMILTON R. FISHBACK.

THE DEXTROSE-TOLERANCE TEST: ITS USE IN THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS. M. WISHNOFSKY, *Arch. Int. Med.* **42**:443, 1928.

The amount of glycosuria during the dextrose tolerance test does not indicate the severity of the diabetes. The true criterion is found in the character of the blood sugar curve.

HAMILTON R. FISHBACK.

A NEW CLINICAL TEST FOR TISSUE THIRST. W. A. THOMAS and E. ANDREWS, *Arch. Int. Med.* **42**:776, 1928.

On dialyzing normal blood serums against hundredth-normal hydrochloric acid, the absorbing power varied from 1 to 9 per cent. Serums from patients with nephritis, uremia and edema of cardiac origin gave hydrophilic values of from 15 to 50 per cent. This value may be due to some foreign protein in the blood or to some change in the colloid dispersion of the normal proteins of the blood.

HAMILTON R. FISHBACK.

DETERMINATION OF SUGAR IN CEREBROSPINAL FLUID BY BENEDICT'S COPPER METHOD. ROGER S. HUBBARD, Clifton M. Bull. **14**:123, 1928.

There are rather marked differences between the spinal fluid sugar when determined by methods as different from each other as are Benedict's copper and picric acid methods, but the differences are not as great as are those found in blood. The copper methods of Benedict and Folin and Wu give almost identical values when applied to spinal fluid, although there are marked differences in the results

when the same methods are applied to blood. It seems probable, therefore, that there are nondextrose-reducing substances in blood, which either do not enter the spinal canal or which pass into the fluid only in relatively small amounts. The range of reducing compounds in the spinal fluid is probably almost exactly the same as is that in blood, namely, 30 mg. per hundred cubic centimeters, but the amounts are decidedly smaller. This difference for Benedict's copper method seems probably to be about 20 mg. per hundred cubic centimeters. The actual range of Benedict's copper reduction method obtained under fasting conditions is probably from about 50 to approximately 80 mg. per hundred cubic centimeters, although a conservative interpretation should be placed on results slightly higher or lower than these limits. Interpretation of high values should almost certainly be made only in connection with blood determinations carried out on samples obtained at the time when the specimens of spinal fluid are taken. Plasma studies should form a more satisfactory basis for such comparisons than do those on whole blood, because there are reducing compounds in the cells which apparently do not penetrate into the plasma, just as there are similar compounds which do not enter the spinal canal from the blood.

## AUTHOR'S SUMMARY.

**SINGLE CELL TECHNIC: A PRESENTATION OF THE PIPETTE METHOD AS A ROUTINE LABORATORY PROCEDURE.** A. H. GEE and G. A. HUNT, J. Bact. **16:327**, 1928.

The pipet method of procuring single cell bacterial cultures is described in a form which can be applied as a routine procedure requiring a minimum of special equipment. Attention is directed to the steps in the technic which are essential for success, and certain refinements are offered. Accessory equipment recently devised by various workers and of service in work with organisms that are difficult to cultivate is reviewed briefly.

## AUTHORS' SUMMARY.

**A GASOMETRIC METHOD FOR DETERMINATION OF REDUCING SUGARS, AND ITS APPLICATION TO ANALYSIS OF BLOOD AND URINE.** D. D. VAN SLYKE and J. A. HAWKINS, J. Biol. Chem. **79:739**, 1928.

"A gasometric method is described for determining reducing sugars. The latter are permitted to react with ferricyanide, of which an amount proportional to the sugar is reduced to ferricyanide. The decrease in ferricyanide caused by the sugar is measured by the decrease in the pressure of  $N_2$  gas observed when the ferricyanide liberates  $N_2$  from hydrazine in the Van Slyke-Neill manometric apparatus. Applications to rapid determination of sugar in blood and urine are described."

## AUTHORS' SUMMARY.

**MEMBRANES FOR ULTRAFILTRATION, OF GRADUATED FINENESS DOWN TO MOLECULAR SIEVES.** J. W. MCBAIN, and S. S. KISTLER, J. General Physiol. **12:187**, 1928.

The writers recommend the use of cellophan for ultrafiltration, and give two methods for decreasing the size of its pores until it becomes a fine molecular sieve. They emphasize the fact that ultrafiltration is a distinct process, bearing little relation to diffusion, dialysis, osmosis, electro-osmosis or thermodynamics.

## H. E. EGGERS.

**METHOD OF STAINING FLAGELLA.** EMIL WEISS, J. Infect. Dis. **43:228**, 1928.

A new method of staining flagella includes the treatment of young cultures with acetic acid (sufficient to make 5 per cent). A drop of this suspension on the slide is allowed to dry untouched, and staining is first produced with a basic dye and then with an acid dye. Useful contrastive stains were saturated gentian or crystal violet and acid green, Löffler's methylene blue (methylthionine

chloride, U. S. P.) or aqueous thionine blue and acid fuchsin, brilliant green and acid fuchsin or acid violet and carbol fuchsin and acid green. This method is also useful for the demonstration of degenerated or phagocytosed bacteria.

AUTHOR'S SUMMARY.

THE HINTON GLYCEROL-CHOLESTEROL TEST FOR SYPHILIS. AUSTIN W. CHEEVER and RUSSELL L. SPLAINE, *New England J. Med.* **199:967**, 1928.

A detailed description of this test as recently modified will be published soon. The technic used by Cheever and Splaine is described by Hinton (*Boston M. & S. J.* **196:993**, 1927). The results obtained in 1,610 cases are discussed. In 260 cases in which discrepant reactions occurred, the Hinton test gave the largest number of positive results in known syphilitic cases and as few false positive reactions in the nonsyphilitic cases as any of the other methods used for comparison, such as the Wassermann test, the Kahn test and the slide test of Kline and Young. The results are interpreted as showing that the Hinton test is a more sensitive test for syphilis than the others. The authors also conclude from their data that a negative reaction to the Hinton test is a safer criterion of cure than a negative Wassermann reaction of the test blood serum.

BLOOD GROUPS AND PATERNITY. G. HASELHORST, *Klin. Wchnschr.* **7:1816**, 1928.

The blood groups O, A, B and AB in 1,000 men were, respectively, 41.10, 41.80, 13.10 and 3.00 per cent; in 3,000 women, they were 39.33, 43.70, 12.73 and 4.23 per cent. Among 750 determinations of mother and child, 400 of which included also the father, there were only two exceptions to the inheritance rules of von Dungern and Hirsfeld and none to the general scheme of Bernstein. A plausible explanation was found for one of these exceptions, but not for the other.

E. F. HIRSCH.



## Society Transactions

### NEW YORK PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Nov. 8, 1928*

HARRISON S. MARTLAND, *President, in the Chair*

DEMONSTRATIONS OF RARE UTERINE TUMORS: MYOMA WITH FATTY CHANGE; LIPOMYOMA; FIBROLIPOSARCOMA; MYXOMYOSARCOMA. ALFRED PLAUT.

*Myoma with Fatty Change.*—This specimen, the soft body of the uterus of a married woman, aged 47, chiefly consisted of a ball-shaped myoma, 12 cm. in diameter. A sausage-shaped continuation of the myoma distended the cervical canal and appeared like a polyp in the external os. The uterine cavity was stretched posteriorly over the tumor. The cut surface was as usual, half gray and half yellow, with a hue similar to that seen in xanthomatous or pseudoxanthomatous foci. The outer and lower parts were more yellow; the inner and upper portions were gray. The structure, however, was the same over the whole cut surface; it was entirely that of a myoma. That was seen much more clearly in the fixed specimen than appeared immediately after operation. Microscopically, most of the muscle cells in the yellow areas were filled with fat droplets; they assumed a brilliant red color with the sudan IV stain. Large and small droplets more or less completely filled the space between the nucleus and the outline of the muscle cell. Pigment was not found. In spite of the frequency of secondary changes in myoma uteri, such fatty infiltration is rather rare.

*Lipomyoma.*—The specimen was a myoma shaped fairly like a ball, 5 cm. in diameter, which was shelled out from the lateral wall of the uterus of a woman, aged 58. The surface and cut surface exhibited small spots obviously of fat tissue. They occupied about one tenth of the cut surface. The myoma tissue was pale gray and firm. The color of the fat tissue was distinctly different from that of the fatty spots in the first case. Microscopically, fat tissue and myoma tissue were intimately mixed. All the fat cells were large; lipoblasts could not be found. The myoma was partly hyalinized. Fat droplets were not seen within the muscle cells. Myometrium was not available for microscopic examination. Such tumors are extremely rare. In the descriptions of the equally rare lipomas of the uterus, the presence of occasional muscle fibers is mentioned. Perhaps such a lipoma represents a later stage of a tumor such as this, with the fat tissue occupying more and more of the original myoma. Among the theories brought forward as to the origin of the fat tissue, the assumption of undifferentiated cells seems the least improbable. Such cells must be capable of differentiating themselves into muscle cells as well as into fat cells. By calling the tumor lipomyoma, one states only that both kinds of tissue are present, without assuming to describe its histogenesis. One is not even certain that a true blastomatous process lies behind this fat tissue. One investigator has compared the process with the development of fat in dystrophia musculorum progressive (Bruenings), and one might, for comparison, think of the adipositas cordis or the fat often found in the obliterated appendix vermiformis.

*Fibroliposarcoma of Uterus.*—At the age of 55, eight years after the menopause, the patient noticed an abdominal swelling. The specimen, as found at operation, was nearly mathematically ball-shaped with a diameter of 12 cm. The uterine cavity was extremely narrow, almost obliterated. Typical yellow adipose tissue occupied most of the cut surface; the remainder, about one third, consisted of pale pink and gray masses resembling connective tissue. The tissues encroached on each other and mixed. The surrounding myometrium had an average thick-

ness of 8 mm. The outlines of the tumor were distinct, although parts of it (fatty ones) reached into the myometrium. Under the microscope, cellular, partly undifferentiated connective tissue was observed with many round cells of large and medium size. The typical round spaces of the fat cells were irregularly distributed through it. In one ovary, a dermoid cyst was present.

*Myxomyosarcoma.*—A married woman, aged 43, noticed an abdominal swelling. This tumor removed three weeks later from the posterior wall of the uterus had a diameter of 12 cm. It was soft and roughly ball-shaped. The cut surface revealed none of the fascicular or globular structures seen in myoma uteri. It was irregularly yellowish gray, and interrupted by many, more or less circumscribed spaces, filled with fluid. This fluid was edema-like in the upper half, while in the lower half it was cloudy and partly bloody. The solid parts were homogeneously glistening. A line of cleavage between tumor and myometrium was easily established. The microscopic picture was that of a spindle cell tumor with wide variation in size, shape, staining qualities, etc. A true myoma-like picture could be found; but an origin from muscle tissue was probable, nevertheless. The homogeneous material separating groups of tumor cells or even single cells gave a positive reaction with mucicarmine, but only when a strong solution was used. Only exceedingly little metachromasia was obtained with polychrome methylene blue. The name given this tumor is meant to indicate the highly probable origin from myoma, the malignant character of the growth and the histochemic nature of the mucin-like material. The tumor has nothing in common with myxoma.

An attempt will be made to examine the patients.

#### DISCUSSION

NICHOLAS ALTER: What criteria did you have for calling the specimen sarcoma?

ALFRED PLAUT: The irregularity of the whole picture. These were all specimens calling for operative intervention. All the women are now in good health several months after operation for myoma uteri.

#### A CASE OF SUBAORTIC STENOSIS. C. E. DE LA CHAPELLE.

Subaortic stenosis (also known as subvalvular stenosis) is rare. In view of this and because of several unusual features, it seemed of sufficient interest to report the following case, which came to necropsy in the Bellevue Hospital mortuary (service of Chief Medical Examiner Dr. Charles Norris, to whom I am indebted for the privilege of presenting the specimen).

A. G., an obese white man, aged 55, was found dead at his home. The previous history was incomplete; the only important fact was that he had been a well-known lightweight prizefighter some twenty to thirty years prior to his death.

The heart was enlarged and weighed 490 Gm. The valves were normal, save for the aortic valve. One centimeter below the aortic cusps, and on a level with the junction of the membranous and muscular portions of the interventricular septum, there was a ridge with a well defined edge. Above, it was continuous with the endocardium of the base of the left ventricle. In this area there was a shelllike formation that blended into the undefended space. At its extremities, where it became shallow, it was continuous with the base of the aortic leaflet of the mitral valve. When the specimen was closed, the conus portion of the left ventricle was transformed into a more or less narrow canal. The circumference of the orifice formed by the anomaly was 6 cm., 2.5 cm. of which was formed by the base of the aortic leaflet of the mitral valve.

The aortic cusps were markedly but uniformly sclerosed and rigid. They were adherent at the commissures for several millimeters. A pearly plaque, characteristic of the gross lesion of syphilitic aortitis, involved the commissure between the right anterior and left anterior cusps. There were several other smooth pearly plaques scattered about the first part of the aorta. The orifices of the coronary arteries were patent. The vessels themselves were moderately sclerosed.

Microscopic examination of the aorta and an aortic cusp revealed the presence of a syphilitic process. The anomalous ridge presented an external layer of what apparently represented hyperplastic and hyalinized endothelial cells derived from the endocardium. The greater part of the anomaly, however, was made up of cells that appeared to be muscle fibers. Some were degenerate, but most of them have undergone hyalinization.

The specimen presented displayed a congenital malformation. The unusual features of this case were the age of the patient, 55 years, and the previous occupation, prizefighting. During his active fighting career, the aortic valves probably were still normal, and although the subaortic stenosis was present at that time, the function of the heart apparently was not impaired much, if any. The aortic valves probably became involved by the syphilitic process at a later period. The lesion in these valves was another unusual feature of the case, since it presented a stenosis rather than the usual insufficiency of the valves due to retraction and widening of the commissures as is so typical of syphilis. The specimen therefore really presented a "double aortic stenosis," the valvular stenosis being an acquired lesion, and the subvalvular stenosis, a congenital one.

(The gross specimen was exhibited, as well as lantern slides of the gross specimen and of sections of the aorta, aortic cusp, interventricular septum and the anomalous stenosis.)

#### DISCUSSION

E. LIBMAN: I have not made a study of this subject, but there are certain points that I would like to make concerning this presentation. This subaortic stenosis is particularly interesting because, as you see from the picture on the screen, it involves the aortic flap of the mitral valve. Occasionally, one sees a congenital membrane below the aortic valves without any stenosis. Last summer, in Amsterdam, Professor de Vries showed me two specimens presenting this condition.

In this case, we have no record of what murmurs, if any, were present. When calcification is present in the aortic flap of the mitral valve, there is apt to be present a systolic murmur, heard louder near the sternum than at the apex. The French call such murmurs *juxta-aperienne*. When there is a definite jutting out of the lime, so that a narrowing is produced, some speak of a mitro-aortic stenosis. Objection has been raised to the use of this term in this way, especially by Gallavardin. It would be of interest to hear what the literature says about the murmurs heard in cases of congenital subaortic stenosis.

The amount of sclerosis in the valve flaps is extremely interesting. Does Dr. de la Chapelle believe that the lesion of the valve is entirely syphilitic? A marked fibrosis in syphilitic aortic flaps usually appears only after they become retroverted. Then there develops a fibrosis from tension in them, and sometimes calcification. I have noted that calcification is less likely to occur in syphilitic valves than in those diseased from other causes.

I draw particular attention to this marked fibrosis because, if the stenosis is congenital, the valves ought to have been protected from strain and secondary fibrosis. There is usually no dilatation of the aorta when a stenosis is present. The question arises whether these valves may have been congenitally diseased, so that there was a congenital stenosis before the syphilitic condition occurred, or whether there was originally a congenital diffuse thickening of the flaps. If I had known before the meeting of the type of lesion that was to be presented, I would have demonstrated a picture of a mitral valve with congenital thickening (myxomatoid) of a whole flap.

HARRISON S. MARTLAND: I was under the impression that in almost all cases of subaortic stenosis the mitral valve was also involved, usually with the production of a mitral stenosis. Is that correct? The aortic cusp of the mitral valve is always thickened in these cases, is it not?

BENJAMIN SACKS: I have never had the opportunity of studying a case of subaortic stenosis. It is interesting to inquire whether this condition might not be due, at times, to an inflammatory lesion. I have recently read of a case

of subaortic stenosis associated with subacute bacterial endocarditis. In such cases, the question would be whether the subaortic stenosis preceded the endocarditis or was the result of it. Inflammatory lesions of rheumatic origin are often seen in the subaortic region on the wall of the interventricular septum, and may be of wide extent. The cases which Dr. Gross and I recently studied did not show any narrowing of this region. The lesion is interesting, and one that Dr. Libman has pointed out in his illustrations many times. This subaortic patch of endocarditis in rheumatic hearts was formerly regarded as a change due to tension, or one related to the aortic insufficiency. The area involved has a dry, wrinkled, corrugated appearance, and in some of the cases the lesions are similar to the auricular lesions described by Dr. MacCallum and Dr. von Glahn. Microscopic sections show not only diffuse inflammatory involvement, but also Aschoff bodies in the deeper layers. As far as the valvular lesion in this case is concerned, I must say that I have never seen a syphilitic valve that showed the amount of commissural fusion which this one did. This change is more frequently seen in rheumatic endocarditis, and I wish to inquire whether sections of the other valves have been made in order to determine the possible presence of a rheumatic lesion in this case, because the aortic valvular stenosis might, perhaps, be better explained on an inflammatory basis of this kind, although a syphilitic etiology is possible.

HARRISON MARTLAND: I am sure that I have seen in syphilitic supravulvar sclerosis an extension to the aortic cusps similar to that seen in this specimen, the cusps being rubbery and markedly thickened, especially on their free edges, with little if any retraction, and hence little regurgitation.

CLARENCE DE LA CHAPELLE: I think Dr. Libman's point about the possibility of this being a diffuse congenital thickening of the aortic valve itself is good. The microscopic picture, however, was that of a syphilitic lesion. I would like to have found another congenital anomaly in this man. As you know, it is not unusual to find a second congenital anomaly in cases of congenital heart disease. He had no other congenital anomaly.

I agree with Dr. Sacks as to the appearance of the aortic valves, and I believe I mentioned that this valvular lesion was contradictory to the usual condition of the valves as found in syphilis. On a gross diagnosis, I would say it was an old rheumatic valve. Unfortunately, I did not make any other microscopic sections. I came across this pronounced syphilitic reaction in the aortic cusp in the first sections cut. There was also a great deal of fibrosis in the cusp. I think one big argument against its being rheumatic is that the mitral and tricuspid valves were practically normal. There was little sclerosis of the mitral valve itself, hardly enough to mention. Our English brethren insist that the mitral valve is involved in 100 per cent of the cases of rheumatic heart. The American figures are about 88 per cent. I think it is important to mention this, particularly in reference to Dr. Martland's question about the association of mitral stenosis with this anomaly. I did not make an extensive examination of the myocardium for rheumatic involvement, for I did not think it was indicated.

As regards bacterial endocarditis, many of the cases of subaortic stenosis are associated with a bacterial lesion, but the probability is that the bacterial lesion was implanted on the stenosis, because of the similarity of the position of the defect as described in these cases. The uniformity of the ridge in this specimen agrees with the evolution of this anomaly as described by Keith; therefore I am afraid that one would have a difficult time in explaining it on the bacterial basis alone. I think the implantation of a bacterial lesion on it is important, especially with reference to the involvement of the mitral valve portion of this malformation. In most of the bacterial cases reported, that part of the mitral valve was involved, probably by continuity.

E. LIBMAN: On looking at the specimen, which has just reached me, I note that the thickening is not nearly as marked as it appeared to be from the photograph, and I therefore withdraw what I said about the possibility of the flaps being congenitally thickened. The lesions can be explained by the syphilitic lesion and partly by chemical changes, the deposit of lime.



## FENESTRATIONS OF THE SEMILUNAR VALVES. ARTHUR N. FOXE.

As my paper is largely statistical, I shall not refer to it entirely. A review of the literature reveals how inadequate is the present understanding of the subject. The literature is scant; numeric statistical studies are lacking, and a review of texts of anatomy and pathology shows much confusion as to the nature and frequency of these defects. The results here summarized follow from a study of 300 successively observed hearts.

One or more fenestrations occurred in 82 per cent of the cases. The aortic valve was involved in 188 cases, the pulmonic in 187 cases; a negligible difference in frequency. However, in an estimate of the total number of fenestrations, the pulmonic exceeded the aortic valve in frequency, whereas in the number of leaflets involved, the reverse was true.

From the statistics compiled, it is evident that fenestrations, which are acquired defects, numerically increase with age up to the fourth decade. On the other hand, patent foramen ovale, a distinct developmental defect, numerically decreases with age. There is no evidence to show that fenestrations are developmental defects. Even an inherent weakness of the endocardial or connective tissue is questionable. The fenestrations are a pathologic result fundamentally mechanical in origin. The few present at birth may be acquired from the mechanical effects of the intra-uterine fetal circulation.

A classification of these defects has not thus far been made. The following is such a classification: mechanical: (a) circulatory (persistent strain of circulation), (b) traumatic and (c) ulcerative (infection plus erosion of current).

The most frequent cause is the persistent strain of the blood current on the valve leaflets. It is questionable whether the perforations of ulcerative endocarditis or trauma (one case of the latter due to a bullet wound) should be included in a classification of fenestrations. An understanding that they are all fundamentally mechanical in origin would justify such a classification.

The most frequent site is adjacent to the attachment of the free edge of the cusp to the aortic intima. The defects may be single or multiple. They are defects in the endocardium that bridges the gaps between the strands of connective tissue stroma. Less frequently the fenestrations occur along the free edge of the valve. As a result of adhesions of the cusps, they may not communicate with the heart cavity, but form, instead, a passage between two sinuses of valsalva. At times they form a veritable network, not without a peculiar anatomic beauty.

Apart from any esoteric pathologic or anatomic import, have they any clinical importance? Clinical data were lacking in so many cases that it was impossible to correlate any of the observations with murmurs, blood pressure readings, etc. However, in two cases the fenestrations were so large and so numerous as to bring to mind the possibility of aortic insufficiency. In one of these, with a non-dilated orifice, the fenestrations occupied at least one half the valve area.

## DISCUSSION

E. LIBMAN: I would like to know the percentage incidence for each five year period.

ARTHUR N. FOXE: There is a defect in these statistics; that is, although age groups are given, each of the groups does not embrace an equal number of hearts; if one bases a conclusion on the cases coming into the Bellevue laboratories there is a larger percentage in the later decades of life. There were forty-two cases observed in persons under 8 years of age, and 258 in those over. There were three fetal hearts, and in this group there were 1.3 per cent fenestrations per heart. One of the three fetuses had fenestrations; two had patent foramen ovale.

E. LIBMAN: I do not have any opinion concerning these fenestrations based on personal studies. In Vienna and in Berlin, we were taught that the fenestrations are due to atrophy. I would like to give you the evidence in the literature against this view. What Dr. Foxe has presented to us would speak largely against the view that the lesions are entirely congenital. It looks as if some of them, at least, in older persons, may be developed late.

My interest in the subject was aroused by a paragraph in the second edition of the "Lectures on Pathological Anatomy" (1874) by Wilks and Moxon. That made me aware of the fact that fenestrations had been claimed to be of congenital origin. Wilks drew attention to the fact that in certain animals (the shark, for example) the semilunar valves are attached to the wall of the aorta by chordae tendineae. He believed that fenestrations are explainable as remnants of such chordae.

Shortly after I had come across this reference, Dr. Gross showed me a heart which I will now demonstrate to you on the screen. I was shown at first only this flap with this structure, which I recognized as a chordae tendinea. I stated what Wilks had written, and was then shown the other two valves with the fenestrations that you readily see.

Last year I came across an article on this subject by Norman Cheevers in *Guy's Hospital Reports* for 1842. He believed that fenestrations are congenital malformations. I will show you reproductions of his illustrations. One picture is that of a combination of fenestrations and a chorda tendinea; the second shows marked fenestration in the heart of a child, 4 years of age. This large defect in the valve certainly appears to be congenital. The third illustration is of the arrangement of the aortic valves in the shark. There are two sets of semilunar valves, one above the other. The upper is like that in man, while the lower is attached by numerous chordae tendineae.

LOUIS GROSS: I must confess that I was worried about the same problem which evidently worried Dr. Libman, that is, with regard to the significance of the statistics which Dr. Foxe presented, and I was not surprised to hear that his figures on the hearts coming from fetuses and from the lower decades of life are rather small as compared to the later decades. I think that his observations are important, and certainly open up a field to be reinvestigated, but the answer will not be given before Dr. Foxe can compare a relatively large number of hearts representing each decade. When comparisons are made between groups approximately equally large and representing each decade, and if more fenestrations are found in the older decades of life than in the younger, it will be of considerable significance. Apart from this, I must say that the belief that these fenestrations are congenital in origin rather than acquired appeals to me much more strongly. If these lesions are due to pressure or mechanical changes, one ought to be able to find near the fenestrations other thickenings and distortions. One does not. One generally finds these flaps with fenestrations thin and delicate, and not showing any other lesions. This argument may not be pertinent, and I am very glad that Dr. Foxe has brought this question to the fore. I do feel, however, that further work ought to be done along the lines indicated.

ALFRED PLAUT: In case the lesions are due to pressure, why are they not much more frequent on the aortic valve than on the pulmonary valve, with the marked differences in pressure at both points?

BENJAMIN SACKS: Only today, I saw a case in which one of the cusps of the aortic valve was almost as large as the other two combined, which were joined together as in the bicuspid aortic valve, but the difference was that the two joined valves, the anterior and the right posterior cusps, were not fused in the usual way. Instead, the commissure was fused for a distance of 4 or 5 mm., and, extending between the commissure and the free edge of the combined cusps, there were chordae-like structures, similar to those which Dr. Libman showed on the screen. In this case, one can only assume that these structures were congenital.

ARTHUR N. FOXE: I see the inadequacy of not having a larger percentage of cases in the younger groups. However, one thing is apparent, that when one examines the hearts of the infants, one observes a marked difference from those of the older groups, and this difference becomes more apparent in the statistical figures.

As to the question why they are not more frequent on the pulmonic than on aortic valves, considering the differences in pressure, it is noteworthy that the

strength of the pulmonic and aortic valves is not exactly the same, and one can distinctly see the differences in density between the leaflets of the aortic and those of the pulmonic valves.

As for the statements that these chordae tendineae prove the theory of a developmental origin, I should like to say that they do not. If you will put any picture showing fenestrations on the screen, I will show the inadequacy of the picture from the anatomic point of view, and that these tendineae are not really chordae tendineae from the genetic standpoint. If you take up the heart of an infant, and hold it to the light, you will rarely find fenestrations; here you will find the endocardium, and through the endocardium you will see strands of fibrous tissue that run in this direction from the attachment of the aorta over to the corpora arantii; these strands run in succession to the corpora arantii. These so-called chordae tendineae are nothing more than the remnants of these connective tissue strands. Here you see two supposed chordae tendineae. They are not chordae tendineae. Gradually pressure effects have destroyed the endothelium, and the result is the development of fenestrations.

THE MUCOSA OF THE INTRAMURAL SEGMENTS OF THE COMMON BILE DUCT AND PANCREATIC DUCTS. BENJAMIN N. BERG.

The arrangement of the mucosae of the intramural segments of the common bile duct and the major and minor pancreatic ducts was studied in dogs. As the ducts entered the duodenum, there was an abrupt transition from a slightly irregular epithelium to a definite fold formation. As the ducts penetrated deeper into the musculature, villi and septums were encountered. At the papillae, long, slender villi were found arranged in parallel rows. The number of mucous glands was greatly increased. The mucosal pattern was practically identical in the three ducts. The following features were noted: (1) a mucous membrane that practically filled the lumen of the duct; (2) a greatly increased surface area with opportunity for increased mucous secretions, and (3) a mechanical arrangement preventing the influx of duodenal contents into the duct system.

DISCUSSION

PAUL KLEMPERER: I would like to ask if Dr. Berg found lymphadenoid tissue in the terminal portion of the common duct. The question is asked because of the observation of Eppinger of swelling of the lymphatic tissue in the common duct in a case of simple catarrhal jaundice. I have examined repeatedly the terminal portion of the common duct for the presence of lymphatic tissue and have never found it.

BENJAMIN B. BERG: No, I never did.

DETERMINATION OF SUSCEPTIBILITY TO ERYSIPELAS BY SKIN TESTING. T. R. MINER.

In the course of the past year at Bellevue Hospital a test for the determination of susceptibility to erysipelas has been employed in a series of 656 persons selected at random from among patients, nurses and interns. The purpose was to determine, first, the incidence of susceptibility and, if possible, some of the factors underlying the apparent lack of resistance among certain persons to this particular form of infection.

The method employed consisted in the intradermal injection into the forearm of 0.1 cc. of a 1:500 dilution of erysipelas toxin. An intradermal injection of physiologic sodium chloride solution was used as a control. The readings were made at the end of twenty-four hours, and the degree of susceptibility was determined by the extent of the local reaction.

The age, sex, race, nationality, habits and occupation were noted, together with the disease from which the patient was suffering at the time and such diseases as the patient had had before the test was made that could be attributed to streptococcal infection, namely, scarlet fever, chorea, rheumatic fever and, especially, erysipelas itself.

The total percentage of the susceptible persons was 43, those in the second, third and fourth decades of life giving the greatest number of positive reactions. Females were found to be more susceptible than males in the ratio of 5 to 4. Jews were found to be more susceptible than any other race. By far the greatest percentages of positive reactions occurred among those who worked outdoors where there are varied and variable climatic conditions. Fatigue and exhaustion over long periods of time were also found to play a part, while the great majority of those who gave positive reactions were of careless habits, debauched and unclean.

Perhaps the most significant fact brought out by the skin tests, however, was the relation of susceptibility to erysipelas following previous attacks of the disease and other diseases of streptococcal origin. Of those tested, 3 per cent had previously had erysipelas, and of these, 70 per cent gave markedly positive reactions. In these, the first attack had occurred from two weeks to eighteen years previous to the time of testing the skin, so that the degree of susceptibility is apparently not dependent on the length of time that has elapsed between the initial and the secondary attacks.

Closely following erysipelas itself as a cause of increased susceptibility in subjects, are rheumatic fever and scarlet fever. It was also noted that patients suffering from acute endocarditis, cellulitis and streptococcal infections of the blood stream gave a high number of positive reactions.

#### DISCUSSION

LOUIS GROSS: I would like to ask Dr. Miner what he took as an index of susceptibility to erysipelas.

T. R. MINER: I took the amount of reaction around the intradermal injection.

LOUIS GROSS: First of all, I would like Dr. Miner to explain why he assumes that a positive reaction from an erysipelas toxin necessarily indicates a susceptibility to the disease. You may recall that Dochez and Stevens, and recently Birkhaug, have been able to show, in the cases of the hemolytic streptococcus of scarlet fever and the anhemolytic streptococcus obtained from cases of rheumatism, respectively, that if you sensitize animals by intraperitoneal injections of the so-called toxins of these organisms the animals pass through several phases. In the first phase, the skin of the animals apparently becomes sensitive to the homologous toxin, and early in the first phase one can neutralize this reaction with the homologous serum. Then they pass through an insensitive stage. If you continue to sensitize them, however, you get a third stage in which any organism of the streptococcus group that they employed will elicit a positive skin reaction, which skin reaction cannot be neutralized. In other words, it appears from their work, if one can draw any generalizations from work with these two organisms, that if animals are sensitized for a long enough period they develop a skin sensitivity to the toxins of many organisms in the related and even in unrelated groups; therefore it is not surprising to me, although it is very interesting, that Dr. Miner was able to confirm this in the human being, but I cannot understand why he believes that those giving a positive reaction are necessarily susceptible to erysipelas.

T. R. MINER: The testing of the skin to demonstrate susceptibility to erysipelas is identical in principle with that of the Schick or the Dick test, and I think the best way I can answer the question is to state the fact that of the many patients in the erysipelas wards at Bellevue whose conditions clinically were diagnosed as erysipelas, not one gave a positive reaction; we are using that observation on the other side of the erysipelas question; that is, it can be used to indicate a negative diagnosis. If we test a patient's skin, and the test is positive, we can definitely say that the patient does not have erysipelas. If the test is negative, we cannot say that the patient does not have erysipelas. Every patient in the wards who was definitely proved to have erysipelas gave a negative reaction in the skin test.



## PHLEGMONOUS GASTRITIS (ERYSIPELAS OF STOMACH?). HARRISON S. MARTLAND.

Recently, I had the opportunity of observing before death, and of finding at autopsy, a case of phlegmonous gastritis of streptococcal origin in which the appearance of the stomach, as seen with the naked eye, suggested the possibility of the condition being erysipelas. The histologic observations were identical with those seen in erysipelas of the skin or that of the mucous membranes. The streptococcus occurring in enormous numbers in the submucosa was sent to Birkhaug for complete identification.

The stomach was taken, at autopsy, from a white woman, aged 72, who had been sick for one week and had died five hours after admission to the hospital. At the beginning of her illness, she was suddenly seized with cramplike pains in the abdomen, localizing in the upper left quadrant. She was nauseated and vomited twice. The pain became intense, the abdomen being distended and tympanitic. A suspicious mass was felt in the left hypochondrium. Only stimulative treatment was given at the hospital. A clinical diagnosis of peritonitis possibly due to a malignant condition of the abdomen was made.

At autopsy, the stomach was greatly distended. Near the pylorus, it felt as if there was a large stenotic growth. The whole stomach wall was leathery and did not collapse. Enlarged glands were not present along the lesser or the greater curvature, and enlargement of periportal nodes was not seen. The esophagus was normal. On opening the stomach, which was empty, a remarkable condition was seen. There was marked thickening, with edema of the stomach wall, most marked in the pyloric half, where the wall was  $\frac{1}{2}$  in. (1.27 cm.) thick. The mucosa was a diffuse scarlet, and showed only an occasional mucosal and submucosal hemorrhage. The rugae were obliterated and ironed out by the edema. Recent or cold ulcers and macroscopic abrasions were not observed. Close inspection of the stomach wall showed that over half of the thickening was due to distention of the submucosa by a watery, purulent exudate. The mucosa was but slightly swollen. In the submucosa, lying between the mucosa and the internal circular muscular coat, which was plainly visible, there was a large amount of grayish, watery, purulent fluid, which could be pressed out. The submucosa had a somewhat honey-combed appearance, owing to a partitioning off of this purulent fluid by connective tissue trabeculae. In places, multiple small abscesses were seen in which the fluid was thicker and more creamy. The muscularis, aside from the presence of edema, was grossly free from pathologic evidence. Over the serosa was a plastic purofibrinous exudate. This suppuration extended diffusely throughout the entire submucosa of the stomach, but was more pronounced in the pyloric half. It was sharply demarcated above by the esophageal orifice and below by the pyloric valve. The mucous membrane of the esophagus and the duodenum was normal. There was considerable purulent fluid in the pelvis and abdominal gutters and an extensive fibropurulent exudate over the stomach and the loops of the small intestine, gently gluing them together in places.

Microscopic sections made through the entire thickness of the stomach wall showed that the mucosa was intact and only slightly edematous; it was practically free from any cellular exudate. The muscularis mucosa was intact, but in places edematous and swollen, and it showed a slight infiltration with lymphocytes and histiocytes. The submucosa was greatly thickened, forming over half the entire thickness of the stomach wall. Its inner portion was comparatively free from cellular exudate but showed enormous edema, the fluid distending the tissues spaces and widely separating them. The little amount of cellular exudate present was composed chiefly of lymphocytes and monocytes. A definite relationship to the lymphatics could not be made out. Few polymorphonuclears were present. As one approached the middle of the submucosa, the exudate became abundant and more polymorphonuclears were present. This became so marked as to form small abscesses. The periphery of these areas was formed chiefly of lymphocytes and monocytes, and the central portions contained chiefly polymorphonuclears. In the center of many of these areas there was extensive necrosis with numerous poly-

morphonuclears and considerable cellular detritus. Gram stains showed numerous streptococci in these areas; they were scant or absent in other portions of the stomach wall. Near the internal circular layer of the muscularis there was a strong defense wall composed of many histiocytes and lymphocytes and few polymorphonuclears. In places, this cellular exudate filtered through the muscle bundles of the muscularis and extended to the serosa, where there was edema with beginning suppurative peritonitis. The muscularis itself was free.

Smears made from the fluid pressed from the submucosa of the stomach showed a great number of gram-positive streptococci.

A case of phlegmonous gastritis has been described, in which the appearance of the stomach is identical with that in most cases of diffuse so-called idiopathic phlegmonous gastritis. That is, there were not any gross lesions of the mucous membrane such as ulcer, carcinoma, abrasions or other injury. The condition was diffuse throughout the entire stomach and almost entirely limited to the submucosa. The diffuse blushing of the mucosa, the ironing out of the rugae by edema and the thick, edematous condition of the submucosa, which was filled with a watery, grayish fluid containing innumerable streptococci with the occasional formation of small abscesses suggested the gross appearance of erysipelas, and the condition was similar in every way to extensive erysipelas of the skin with cellulitis of the subcutaneous tissues. The sharp demarcation of the suppurative process in this case by both the cardiac orifice and the pylorus, areas both of which have a mucosa that is rather tightly bound down, was similar, for instance, to the sharp demarcation and stoppage of facial erysipelas at the lower border of the mandible.

Histologic examination showed the lesion almost entirely confined to the submucosa. It was characterized by extensive boggy edema, in which the cellular exudate was composed chiefly of lymphocytes and monocytes. The polymorphonuclears were abundant only in the central areas, in which formation of abscesses had occurred, and in which there was necrosis, cell detritus and innumerable streptococci. This histologic picture is identical with that seen in erysipelas.

(An agar slant containing a pure culture of a gram-positive hemolytic streptococcus, recovered from the submucosa after autopsy by Dr. Lloyd Riggs, was sent to Dr. Konrad E. Birkhaug, associate professor of bacteriology at the University of Rochester, N. Y., for identification. At the time of the presentation, Dr. Birkhaug's opinion had not been received. A complete identification of the streptococcus as belonging to the serologic types of *Streptococcus erysipelatis* was later made by Dr. Birkhaug. The strain was unsuitable for agglutination because of its quick spontaneous precipitation in broth during the first ten hours of growth. He then resorted to absorption of known antibodies of *S. erysipelatis* and found that the strain removed the agglutinins for three of four of his standard strains of *S. erysipelatis*, and removed only to a slight extent the agglutinins from an antiserum of *Streptococcus scarlatinae*. The strain also gave rise to a production of toxin in Douglas' tryptic digest broth. In a series of titrations in the skin of persons susceptible to the toxin of *S. erysipelatis*, he found that a potent exotoxin was produced, 1 cc. of which contained more than 10,000 skin test doses. In proper dilutions with the antitoxin of *S. erysipelatis*, this toxin was completely neutralized. As a result of Dr. Birkhaug's painstaking confirmation, this case is reported in full as one of erysipelas of the stomach.)

#### DISCUSSION

PAUL KLEMPERER: Phlegmonous gastritis is actually rare. I still remember a specimen shown us when I was a student. It was an impressive picture. The last time I observed a case was years ago in the New York Post-Graduate Hospital. In that case, there was a small carcinoma at the cardia. The submucosa was markedly thickened, and on the serosa the lymph vessels stood out distinctly as yellow strands. This was due to their filling with polymorphonuclear leukocytes. The infiltration of the submucosa was also leukocytic. In addition, I recall another case in which only a part of the stomach was phlegmonous. In the vicinity

of a carcinoma there was an area from 3 to 4 cm. wide, which contained pus. I think the question can be brought up again whether it is possible for patients with phlegmonous gastritis to recover and whether cases of the benign leather-bottle type could not be the result of such an occurrence.

NICHOLAS ALTER: There was a case at the Post-Graduate Hospital in which an operation for pyloric obstruction was performed. In that case, the stomach was uniformly thickened and presented the picture of a leather-bottle stomach. The pyloric region was greatly hypertrophied. Resection of the stomach was done, and the patient recovered. The stomach did not show any ulceration, but a uniform thickening of the wall, and the coats were considerably hypertrophied, mostly the muscle. The submucosa was edematous and fibrous, and the mucosa swollen. The microscopic picture showed a marked infiltration with eosinophils; neutrophils were absent. The condition was diagnosed as a subacute phlegmonous gastritis. The patient made a good recovery, and is still well. I make this remark only to answer Dr. Klemperer's question as to whether these conditions ever heal and result in a so-called benign linitis plastica.

BENJAMIN SACKS: In the pathologic museum at Mount Sinai Hospital there is a specimen of phlegmonous gastritis, to which it was Dr. Libman's practice to refer as erysipelas of the stomach.

HARRISON MARTLAND: Evidently there are various types of phlegmonous gastritis, according to what we have heard. In Dr. Klemperer's case, it was probably secondary to carcinoma, and in this respect his case is similar to some of the cases described in the literature. The cellular elements in the exudate were chiefly polymorphonuclears in contradistinction to their scarcity in my case. In Dr. Alter's case the condition was evidently more of a subacute process. Eosinophils were not present in my case. The histologic picture, as I have tried to describe it, was similar to that seen in erysipelas of the skin. The polymorphonuclears were not so abundant as the lymphocytes and the histiocytes, and the process was almost entirely limited to the submucosa. If the streptococcus isolated from my case can be positively identified as belonging to the group of *Streptococcus erysipelatis*, I believe that, taken in conjunction with the gross appearance of the stomach and the character and location of the exudate microscopic examination, the condition warrants a diagnosis of erysipelas of the stomach.

#### DEMONSTRATION OF FOUR CASES OF MENINGOCOCCUS SEPTICEMIA WITHOUT MENINGITIS. PAUL KLEMPERER.

These cases occurred in children of 4 and 14 months and of 4 and 14 years of age. The clinical course was that of a fulminating disease of from twelve to fourteen hours' duration, starting with vomiting and fever. All the cases showed petechial spots on the skin, but only in the two infants was the clinical picture dominated by the purpuric eruptions. The necropsy of these two cases revealed a hemorrhagic infarction of both suprarenal glands. The two other cases showed multiple ecchymoses of the serous membranes, mainly on the peritoneal surface, and small petechiae of the mucous membranes of the gastro-intestinal tract, ureters and bladder. The mesenteric lymph nodes were swollen and hemorrhagic. The results of the bacteriologic examination of heart blood, spleen and spinal fluid were negative. The latter was perfectly clear.

The histologic examination revealed the presence of large quantities of gram-negative diplococci within the small arteries, arterioles and capillaries of the corium, frequently phagocytosed by leukocytes. There was extravasation of blood around the capillaries and often a mild infiltration by polymorphonuclear leukocytes and histiocytes. Within the submucosa of the intestinal tract, foci of perivascular leukocytic infiltration and hemorrhage were found. Here the small arteries showed circumscribed destruction of the wall with localized endothelial proliferation. Within such foci, gram-negative diplococci were found. There were also circumscribed lesions within the myocardium consisting of polymorphonuclear leukocytic infiltration and necrosis of muscle fibers, which also contained the same organism.

The suprarenal glands showed only an enormous congestion of the cortical capillaries and diffuse extravasation of blood.

## DISCUSSION

J. H. GLOBUS: The main facts have already been presented. You were told of the clinical manifestations and the general anatomic alterations and the lack of any evidence of pathologic changes in the brain. To recapitulate, first let me stress the fact that the cases all showed definite neurologic manifestations. They were all regarded clinically as neurologic cases. They all started acutely with symptoms pointing to involvement of the central nervous system: vomiting, convulsion, deep stupor and some bulbar signs. They all resulted fatally within the short period of from twelve to fourteen hours. They were all regarded at the time of autopsy as instances of poliomyelitis, because they occurred at the time when an epidemic of poliomyelitis was regarded as occurring in the city. Only when we began to study them histologically was doubt aroused as to the diagnosis of poliomyelitis, and we began to look around for some other explanation for the grave neurologic picture.

I have here three slides. The first shows only one thing—I believe it is a positive sign: the marked distention of the perivascular spaces with the marked retraction of the surrounding tissue, leaving behind some of the glia fibers still attached to the vessel wall. This distention is apparently due to the marked edema. Another change is the marked increase in the number of oligodendroglia cells; the latter have a clear area around the nucleus—a clear perinuclear area. This is not just an edematous space, such as is found in a toxic degenerative process of the brain. It is part of the cell body, and Penfield described this peculiar change in the glia cells as an acute swelling of the oligodendroglia.

In another section from another case, we see a marked distention of the perivascular space, with a number of oligodendroglia cells migrating toward the vessel wall. It is also a common manifestation of toxic degenerative changes in the brain.

Here is another preparation showing the only vessel found in the study of almost forty or fifty different blocks taken from various portions of the brain—the only vessel which shows moderate perivascular infiltration. This was the only section in the entire group of cases—the only section out of a total number of forty blocks—with an inflammatory lesion in the meninges.

With these few facts in mind, I should like to call to your attention a paper read by Symmers and Brown three years ago. They described a disease as acute serous encephalitis. They described changes of just the type I have shown you, with no perivascular infiltrations, with no evidence of meningeal involvement, with nothing but distention of the perivascular spaces and edema of the brain. Clinically, all of these cases, eleven or twelve, were true to type: an acute onset, fulminating course, convulsions, various bulbar symptoms and finally deep stupor and death within the short period of from twenty-four to forty-eight hours. Symmers and Brown regarded these cases as an extremely acute fulminating type of acute epidemic encephalitis. Under the circumstances, it was perhaps right to group them as epidemic encephalitis, but I think we may put another interpretation on them; for here we have a clinical picture and anatomic manifestations exactly of the type described by Symmers and Brown, but, in addition, we have evidence of a meningococcemia. The changes in the brain are apparently secondary to a general meningococcemia.

DR. GOLDBURG: Could not this picture and the pathologic changes in the brain occur with any general bacteriemia?

J. H. GLOBUS: I have said that the picture in the brain may occur in any form of bacteriemia or toxemia, and is not pathognomonic for meningococcemia.

E. LIBMAN: In cases as severe as those described by Dr. Klemperer, I would have looked for positive results in the blood cultures. Perhaps a sufficiently large amount of blood could not be withdrawn. In some of these cases the diagnosis may be made with ease by puncturing the lesions of the skin and staining



the material obtained, or by studying stained sections of them. The earliest results obtained by an examination of the blood obtained by puncture were those of Netter and his pupils. Ludwig Pick was the first to find the cocci in stained sections of the hemorrhagic lesions.

In some cases of general meningococcus infection in infants, the lesions are firm, like some of the lesions seen in cases of scurvy, and a mistake in diagnosis may easily occur. In cases of meningitis in infants, rigidity of the neck may be absent. The same is true of cerebrospinal meningitis in old people, but to a less extent than in infants.

PAUL KLEMPERER: In two cases a large amount of blood was taken for culture, with negative results; in one case, 30 cc., taken immediately after death, was cultivated but remained sterile, and in this case an innumerable number of cocci were found within the blood vessels of the skin and even in smears taken after death. It seems as though the cocci die rapidly within the circulation. I examined petechial spots in two other cases of meningococcus septicemia without meningitis in which the patients recovered after treatment, and in these cases meningococci were not present within the vessels; but I found the same vascular changes as in the case with cocci. Apparently, the meningococci may disappear early after having produced the vascular lesions.

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### CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, Nov. 12, 1928*

ESMOND R. LONG, *President, in the Chair*

#### THE RETICULO-ENDOTHELIAL SYSTEM IN *BARTONELLA* INFECTIONS OF ALBINO RATS. PAUL R. CANNON and PRESTON H. McCLELLAND.

The significance of the reticulo-endothelial system as a mechanism of defense against infections has been emphasized with increasing frequency during recent years. Most studies have dealt with its relationship to antibody production, and comparatively few attempts have been made to determine the rôle of this system in its reactions to actual disease conditions. *Bartonella* infections of albino rats, therefore, appeared to offer an unusual opportunity for such a study.

The spleen ranks first of the organs of the reticulo-endothelial system among mammals as the one richest in histiocytes. But even here, there appear to be differences in species as to the relative amount. Krumbhaar has recently shown that when the ratio of the spleen weight to the body weight is used as an index, the spleen is relatively of more significance in man, the dog and the rat, less so in the monkey and the guinea-pig and least in the cat and the rabbit. It is suggestive that most of the earlier work on the effects of splenectomy on antibody formation was done with rabbits and guinea-pigs, animals in which the spleen, quantitatively, appears to be of least significance.

The so-called *Bartonella* anemia of rats offers perhaps the most outstanding example of the dominant importance of the spleen in controlling a latent infection. This anemia occurs in infected rats after the removal of the spleen, due, presumably, to a recrudescence of the *Bartonella virus*. The removal of one or both suprarenal glands, one or both testes, the omentum, the cerebrum or the thyroid gland has no effect; splenectomy, however, causes the typical anemia. One third of the spleen appears to protect. When the pedicle of the spleen is ligated, the organ excised and placed in the peritoneal cavity, the anemia develops as with splenectomy, indicating the necessity of an intact blood supply to control the virus.

The size of the spleen is significant in infected animals as compared with uninfected ones. The average ratio of the spleen weight to the body weight for eighty-four rats infected with the *Bartonella virus* is 0.74 per cent. My figures for thirty-four uninfected Wistar Institute strain animals is 0.25 per cent. The

differences between the ratio of the spleen weight to the body weight in rats infected with *Bartonella* and normal uninfected rats is so striking that it is frequently possible to tell by the splenomegaly alone whether or not the animal is infected.

Histologically, there is definite evidence of the reaction of the reticulo-endothelium of the spleen to *Bartonella* infection. Splens from normal uninfected Wistar strain rats are small and firm, and the splenic follicles are compact and composed mainly of lymphocytes, with only a slight hyperplasia of the centers of the follicles and without mitosis. Also, there is a narrow marginal zone of histiocytic tissue merging into the splenic pulp. On the other hand, splens from animals infected with *Bartonella* are large and fleshy; microscopically, the splenic follicles are large and hyperplastic as shown by the conspicuous germinal centers with many mitotic figures, together with a broad marginal zone which fuses with the prominent splenic pulp.

There can be little question, therefore, that the spleen in some way keeps the *Bartonella* virus under control as a latent infection. When this inhibitive influence is removed, the virus apparently develops rapidly with the resulting acute anemia. It is conceivable that the spleen, as an important part of the reticulo-endothelial system, exerts its controlling effect either by phagocytosis of the *Bartonella* virus at a constant rate, by the formation of antibodies of some type which restrain the development or destroy the organisms, or by both. Thus, when the balance is disturbed between the offensive powers of the organism and the defensive mechanisms of the host, the infection flares up and the anemia results. It is evident, therefore, that the "factor of safety" resides in the spleen, equalling approximately two thirds of this organ; the removal of this factor of safety allows the disease to progress.

If these assumptions are correct, saturation of the cells of the reticulo-endothelial system as a whole to as marked a degree as possible with particulate matter should lead to similar results. With this in view, suspensions of Higgins' india ink in isotonic salt solution were injected into normal rats and into others with the *Bartonella* virus. The results demonstrated clearly that adequate blockade of the reticulo-endothelial system in rats infected with *Bartonella* is followed by a relapse of *Bartonella* infection with the development of anemia as with splenectomy. In order to block this system successfully, however, a maximum of material must be injected within a short time so as to prevent a compensation by regeneration of the cells. Intravenous injections of suspensions of india ink, twice daily, apparently prevented this. Under these conditions, animals infected with the *Bartonella* virus as a latent natural infection developed the typical anemia, whereas normal uninfected Wistar strain rats remained practically normal.

These experiments demonstrate the importance of the spleen in a mammal as an organ of defense against an infectious disease in a latent stage. Furthermore, they indicate the influence of the reticulo-endothelial system as a whole in protecting the host against infection.

#### DISCUSSION

FRANK A. MCJUNKIN: Was the phagocytic activity of the splenic cells as great without as with the carbon particles? Cells stimulated with trypan blue, although large, take up much greater quantities of particulate matter than those not so stimulated.

HARRY A. SINGER: Does a vitamin deficient diet cause the *Bartonella* type of anemia?

R. H. JAFFE: I was unable to cause mobilization of the *Bartonella* virus by deficient diets. Have studies been made to find the latent focus of the *Bartonella* virus?

P. R. CANNON: We did not kill the rats immediately after injecting the carbon, so we are unable to say anything about the erythrophagocytosis. Koessler and Maurer fed vitamin deficient diets to rats, but the resulting anemia is unlike that caused by *Bartonella*. With a diet deficient in vitamin B a *Bartonella* relapse

has not been obtained. By methods for demonstrating the *Rickettsia* bodies attempts are being made to find the latent foci.

E. R. LONG: These studies indicate the hazards of using animals at random, because of such latent infections.

STUDIES ON AN ORGANISM ISOLATED FROM THE PAROTID DUCT IN EPIDEMIC PAROTITIS. RUTH E. TAYLOR.

The results are reported from cultures of parotid secretion in thirty-one cases of mumps and in ten control cases. A green-producing streptococcus was found in 83.9 per cent of the cases of mumps. The organism was not found in any of the control cases. The parotid secretions were examined for the spirochete described by Kermorgant (abstr., J. A. M. A. **85:392** [Aug. 1] 1925) but none was found.

Attempts to demonstrate a relationship between the green streptococcus and mumps by means of immune reactions failed. Herb's (Arch Int. Med. **4:201** [Sept.] 1909) results as to experimental parotitis were not confirmed, although the organism she described resembled that found in this series culturally and morphologically. The organism which was isolated from the cases studied was shown to be pathogenic for cats, but no convincing experimental mumps was produced in these or in other animals.

DUBOIS' SEQUESTRUMS (NONSYPHILITIC) OF THE THYMUS. E. L. BENJAMIN.

Dubois' abscess of the thymus gland was first described as a product of congenital syphilis, in 1850. Hammar and Hart, Tuve, Eberle and Oliver also believed them to be the result of a congenital syphilitic vascular disturbance. The presence of *Spirochaeta pallida* was demonstrated by Simmonds and Schridde. Hammar spoke of them as sequestrum cysts (circumscribed regions of necrosis of the parenchyma of the thymus) lined by epithelium derived from the ectodermal reticulum. Eberle believed them to be dilated epithelial channels, remnants of the thymus anlage, with a subsequent collection of pus in these channels. Chiari and Schlesinger held the opinion that the abscess was a cyst formed by Hassall's bodies invading the thymus tissue. Materna described a Dubois abscess in the thymus of an African negro, aged 24, who was suffering from relapsing fever. There were spirochetes (Duttoni) in the wall of the abscess. This case was questioned by Lubarach and Schmincke.

Dr. R. H. Jaffe performed an autopsy on the body of a full-term, white, male infant, aged 3 days, twenty-two hours after death. Clinically, the infant had symptomatic hemorrhagic purpura immediately after ligation of the umbilical cord. The presence of disseminated petechial hemorrhages in the skin, mucous membranes and leptomeninges; hemorrhagic extravasations in the lungs, liver and kidneys; multiple Dubois' sequestrum abscesses of the thymus gland; hyperplasia of the spleen (29 Gm.); hyperplasia of the mesenteric and peribiliary lymph glands, and fibrinous perisplenitis and icterus established the diagnosis of symptomatic purpura hemorrhagica.

The thymus weighed 15 Gm., was dark red, firm and measured 6 by 4.5 by 15 cm. On the surfaces made by cutting there were numerous irregular soft yellow regions of necrosis, varying in size from that of a pinpoint to 2 by 12 mm. in diameter. Microscopically, the normal structure of the thymus was obscured, being composed of a variety of myeloid, lymphoid and nucleated red cells. In the yellow places there was a coagulation necrosis of the parenchyma with calcium deposits. The necrotic lymphocytes were visible, and a leukocytic reaction was absent. These foci were sharply demarcated and surrounded by reticulum cells arranged in several layers. The smallest foci were devoid of such a lining. Spirochetes were not found in the thymus, spleen or suprarenal glands. Specific syphilitic lesions were absent.

The mother, aged 25, was living and well. This child had been her third full-term child. The other two were living and well, the youngest 1 year old. The

only pertinent data in the maternal history were a thyrotoxicosis from the second to the seventh month of this pregnancy, the petechia reaction of the skin after the application of a constrictor (two days post partum), the escape of a brown amniotic fluid when the membranes were ruptured, and the absence of any signs of syphilis.

The Dubois' sequestrums apparently were not caused by syphilis but were the result of sepsis developing from an intra-uterine infection, possibly associated in some manner with the thyrotoxic crisis of the gravid mother, as evidenced by the syndrome of symptomatic purpura hemorrhagica.

#### SPONTANEOUS RUPTURE OF THE AORTA. RICHARD A. LIFVENDAHL.

Two specimens with spontaneous rupture of the aorta were presented. In both the lesion occurred one and one-half fingers above the aortic cusps. The gross appearance of the vessels were those of slight atheromatous changes, without wrinkling or puckering of the intima; however, the histologic examination revealed typical syphilitic alterations resulting in marked diminution of the functional capacity of the muscular and elastic tissue structures. Perforation occurred into the pericardial sacs, which were markedly distended by blood. Arteriosclerosis was generalized, but most marked in the kidneys, with secondary hypertrophy of the heart. Clinically, both patients had a sudden onset of severe precordial pain and dyspnea, also an elevated blood pressure. The importance of careful microscopic examination of different portions of the aorta was emphasized. The previous literature and the etiologic factors were discussed.

#### DISCUSSION

H. A. SINGER: Why are the spontaneous ruptures of the aorta in the first portion of the arch, as you say, and at the aortic end of the ductus Botalli? What is the hydrostatic pressure necessary to rupture the aorta?

P. R. CANNON: Were these patients under active antisyphilitic treatment?

R. H. JAFFE: The predilection sites for rupture are at the two fixed places of the aorta.

E. R. LONG: Is there a possibility that these lesions are rheumatic in origin instead of syphilitic?

R. A. LIFVENDAHL: Active antisyphilitic treatment was not in use. With dead aortic tissues 1,074 mm. of mercury has been reported necessary for rupture.



## Book Reviews

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LECTURES ON CONDITIONED REFLEXES. Thirty-five years of Objective Study of the Higher Nervous Activity of Animals. By IVAN PETROVITCH PAVLOV, M.D., Director of the Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences; formerly Professor of Physiology, Military Medical Academy, Leningrad. Translated from the Russian by W. Horsley Grant, M.D., B.Sc., with the collaboration of G. Volborth, M.D. Price, \$6.50. Pp. 414, with bibliography and index. New York: International Publishers, 1928.

Pavlov is universally recognized as the pathfinder and leading experimental explorer in the field of nervous physiology and animal and human behavior, that is now considered under the term "conditioned reflexes." Conditioned reflexes are those associations developed after birth as a result of the individual experience and learning of the person or animal as distinct from the simpler and more or less invariable reflexes that are laid down in the structural relations and are therefore inborn. The problem of the analysis and control of conditioned reflexes is therefore of the highest practical importance for educational progress and social control.

The present volume is a translation from the Russian of a series of papers and addresses delivered by Pavlov before various medical and scientific organizations since as early as 1903. It is not, therefore, a book or monograph in the usual sense, containing progressive development of the whole theme. Since it is a translation of different addresses based on research work by students of Pavlov in his own laboratory, there is necessarily a good deal of repetition and overlapping in the different chapters.

The greatest shortcoming in the book, however, is the practically complete absence of references to investigations in the same field but in laboratories other than Pavlov's. These parallel investigations usually confirmed but sometimes disagreed with Pavlov's observations in particular lines and frequently there were different interpretations from those of Pavlov. It would have been interesting and valuable to have had the review and reaction of the aged investigator to the entire aspect of conditioned reflexes up to the year 1928. One must be grateful, however, to have at least the main body of the contributions from Pavlov's own laboratory accessible in English.

There is an interesting initial chapter dealing with the life and education of Pavlov. This biographical sketch and the prefaces occupy the first forty-six pages of the book. The bibliography at the end contains a fairly complete citation of all the publications on the subject of conditioned reflexes from Pavlov's own laboratory in Petrograd. It is interesting to note that practically all these publications appear under the names of Pavlov's students; only occasionally does Pavlov's own name appear on a title. On examination of this final volume by the 80 year old investigator, the reader who recalls Pavlov's first researches on the digestive glands for which he received the first Nobel prize awarded in the medical sciences, is impressed with the continued high quality and mental activity disclosed. He is also impressed with the fact that Pavlov has become more speculative and philosophical with advancing years. This adds to the interest which the book has for the general reader, but it scarcely adds to the progress of objective science. The two short chapters on "The Reflexes of Purpose," and "The Reflexes of Freedom" are an instance of this fact. They contain interesting speculations but virtually no objective experimentation that would warrant their inclusion in a monograph on experimental science.

The present volume is one of great interest to the physician, the biologist, the educator, the psychologist and, in fact, to every educated man. The book is not in any sense the final word. On some phases of the subject, parallel investigations in other laboratories have questioned facts and nullified interpretations found

in the present volume. That is to be expected in a field as complex and new as that of conditioned reflexes. The critical reader, while not overlooking these defects, will forget them in contemplating, as Professor Cannon says, "the splendid example of industry and devotion to science which the first explorer in the field of conditioned reflexes has given during his long life, and this will be an incentive to those who follow after him and push further into the unknown."

UEBER DAS PROBLEM DER BÖSARTIGEN GESCHWÜLSTE. EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG. VON PROFESSOR DR. LOTHAR HEIDENHAIN. Paper. Price, 27 marks. Pp. 153, with 141 illustrations. Berlin: Julius Springer, 1928.

Experimental oncology of today is dominated by two essential facts: (1) cancer can be induced by multiple factors such as tar, arsenic, aniline, soot, roentgen rays, embryonic tissue, nematodes, and bacteria and (2) cancer is "specific," that is, the disease cannot be transmitted from one animal species to another. Even more, within the same species, such as chicken, pigeon and duck, experiments on transmission of the disease have failed up to the present time. Heidenhain in his monograph emphatically states that cancer is infectious in origin being always caused by one living germ. He also affirms that he was able to transmit cancer from man to mouse and that cancer and sarcoma are caused by one and the same factor. In his opinion, the occurrence of one or the other variety of tumor depends on whether the causative agent happened to attack the epithelium or the mesenchymal tissue.

Heidenhain assumes *a priori* that the cancerogenous virus is enclosed within the tumor cells, and he gives his method of "freeing" it, which is as follows: One gram of tumor tissue mixed with 9 cm. of physiologic sodium chloride is ground in a meat grinder. This is overlaid with a layer of toluene and kept for ten days in the incubator at 37 C., after which period the incubated mixture (Wärme-Autolisate, or W-Autole) represents a "formless detritus" ready for use. One-half cubic centimeter of this W-Autole is then injected into the inner surface of the thigh of the mouse, or 0.2 cc. in the liver or peritoneum, respectively.

The material as referred to consisted of tissue from cancer in man, mammary cancer in most instances, which was used on over 2,000 mice. (The statistics are only preliminary.) Of this number about 7 per cent developed tumors which Heidenhain considers as being malignant in nature, being of course produced by the "Autole."

The experiments are interesting in many other ways: 1. The tumor never developed at the site of inoculation, but in organs or structures far remote from the point of inoculation, which is due to "the lymphatic or hematogenous transmission of the virus." 2. Most of the obtained tumors were sarcomas. 3. Only a few tumors gave metastases (Nur wenige Male hatten wir dies Glück . . . to find metastases). 4. The transmitted tumor in the mouse did not usually resemble the mother tumor. 5. Autolysates from carcinomas gave rise to sarcomas and vice versa:

That cancer can be induced by bacteria (which probably play rather a pre-disposing than a determining rôle for the development of a malignant disease) was referred to in this treatise and is recognized by every observer. But the notion that the essential cause of cancer in general is a microscopic virus was not borne out by any research up to the present time. Heidenhain's work does not add any new data to this problem. In the first place, the small percentage of positive results obtained by him do not warrant sweeping conclusions. In the second place, possibility that the tumors in Heidenhain's stock of mice were of spontaneous origin cannot be excluded. Finally, a close examination of the abundant photomicrographs, which illustrate the luxuriously edited monograph, reveals, in many instances, ambiguity as to the blastomatous nature of the condition found by the author.

A SHORT HISTORY OF MEDICINE, INTRODUCING MEDICAL PRINCIPLES TO STUDENTS AND NON-MEDICAL READERS. CHARLES SINGER, M.D., D. Litt., Oxford Fellow of the Royal College of Physicians of London and Lecturer on the History of Medicine in the University of London. Price \$3. Pp. 368, with 142 illustrations. New York: Oxford University Press, 1928.

The purpose of the author is to give a simple, elementary account of the history of medicine as a science. The book is divided into six parts that deal with the following periods: Ancient Greece (to about 300 B.C.); the heirs of Greece (300 B.C. to about A.D. 200); the Middle Ages (A.D. 200 to 1500); the rebirth of science (1500-1700); the period of consolidation (1700 to 1825), and the period of scientific subdivision (1825—). More than half of the book is devoted to modern medicine.

The story of the scientific side of medicine is told lucidly and interestingly. Stress is laid on the development of the underlying principles rather than on actual practice. Consequently, the biographical element and details of the status and training of physicians are kept in the background.

In the preface, the author invites corrections or suggestions. In response, it may be pointed out that the statements about the cause of yellow fever need revision; that August von Wassermann and Alphonse Laveran, listed as living, are dead, and that it is surprising that the scientific side of dentistry did not receive any consideration.

The illustrations are taken from many sources; they are all instructive and some are of unusual interest. Dr. Singer's work should attract the medical reader as well as educated persons without special medical knowledge. It is warmly recommended to the medical student and to the young physician.

AUSGEWÄHLTE SCHRIFTEN ZUR TUBERKULOSEPATHOLOGIE. By K. E. RANKE. Edited with an introduction by W. Pagel and M. Pagel. Price, 20 marks. Pp. 236, with 25 illustrations. Berlin: Julius Springer, 1928.

The plan of Ranke to collect his scattered investigations and treatises on tuberculosis in monograph form, prevented by his untimely death in 1926, has been carried out in part by admiring colleagues. The two Pagels have selected from Ranke's numerous writings those in which he developed the doctrine of the primary complex and three stages in tuberculosis. The investigations and line of reasoning which carried Ranke from pure morphology to far-reaching views on immunity in tuberculosis have stimulated a great deal of discussion and controversy. The Pagels point out that this has been based frequently on an inaccurate knowledge of Ranke's own views, much of his earlier work not being readily accessible. The present volume is put out with the intention of obviating this difficulty. Slight changes from the original publications are indicated by italics, and only those changes are included which Ranke himself had intended. The volume, aside from its value as a collection of selected writings from the pen of a great phthisiologist, should fulfil the stated purpose of the editors.

## Books Received

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**CONSTITUTIONAL INADEQUACIES: An Introduction to the Study of Abnormal Constitutions.** By Nicola Pende, M.D., Professor of Clinical Medicine, Royal University of Genoa, Italy. Translated by Sante Naccarati, M.D., Sc.D., Ph.D., Associate Professor of Nervous and Mental Diseases, New York Post-Graduate Medical School. With a Foreword by George Draper, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, and Chief of Constitution Clinic, Presbyterian Hospital, New York City. Cloth. Price, \$3.50. Pp. 270, with illustrations. Philadelphia: Lea & Febiger, 1928.

**ORGANIC LABORATORY METHODS BY THE LATE PROFESSOR LASSAR-COHN:** An Authorized Translation from the General Part of the Fifth Revised Edition. By Ralph E. Oesper, Associate Professor of Analytical Chemistry, University of Cincinnati, Edited by Roger Adams, University of Illinois, and Hans T. Clarke, formerly of the Eastman Kodak Company. Number two of The World Wide Chemical Series edited by E. Emmet Reid, Professor of Organic Chemistry, The Johns Hopkins University. Price, \$6.50. Pp. 458, with illustrations. Baltimore: Williams & Wilkins Company, 1928.

**BULLETIN OF THE NATIONAL RESEARCH COUNCIL, NUMBER 66:** Funds Available in the United States for the Support and Encouragement of Research in Science and its Technologies. Second Edition. Compiled for Research Information Service by Callie Hull and Clarence J. West. Price, \$1. Pp. 90. Washington, D. C.: The National Research Council of The National Academy of Sciences, 1928.

**BULLETIN OF THE NATIONAL RESEARCH COUNCIL, NUMBER 65:** Bibliography of Bibliographies on Psychology from 1900 to 1927. Compiled by C. M. Louttit for the Research Information Service of the National Research Council. Price, \$1.50. Pp. 108. Washington, D. C.: The National Research Council of The National Academy of Sciences, 1928.

**A SHORT HISTORY OF MEDICINE, INTRODUCING MEDICAL PRINCIPLES TO STUDENTS AND NONMEDICAL READERS.** By Charles Singer, M.A., M.D., D.Litt., Oxford, Fellow of the Royal College of Physicians of London, Lecturer on the History of Medicine in the University of London. Price, \$3. Pp. 368. New York: Oxford University Press, 1928.

**METHODS AND PROBLEMS OF MEDICAL EDUCATION, SERIES XI.** Intended for distribution to teachers and administrators in medical schools and hospitals. Separate reprints and a limited number of volumes are distributed gratis by The Rockefeller Foundation. Pp. 263. New York: Division of Medical Education, The Rockefeller Foundation, 1928.

**ABSTRACTS OF THESES IN SCIENCE, SERIES V.** Ogden Graduate School of Science. Submitted to the Graduate Faculty of the University of Chicago for the degree of Doctor of Philosophy, from September, 1926, to June, 1927. Price \$3. Pp. 461. Chicago: The University of Chicago Press.

**ÉTUDE DE LA RÉACTION DE VERNES A LA RÉSORCINE DANS LE DIAGNOSTIC ET LE PROGNOSTIC DES TUBERCULOSES.** Comparaison avec la réaction de fixation. André Breton, ancien interne des Hôpitaux de Lille, Préparateur a L'Institut Pasteur. Pp. 150. Paris: Masson & Cie, 1928.

**CONTRIBUTIONS TO THE STUDY OF TUBERCULOSIS.** By the Research Department, National Jewish Hospital, Denver. No. VIII. Pp. 510. Denver, 1927.